

Evaluating the effect of oxytocin or carbetocin combined with flunixin meglumine administration and uterine lavage on the treatment of persistent-breeding induced endometritis in Dare-shuri mares

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Received: 02.10.2024

Accepted: 21.11.2024

Abstract

Persistent-breeding induced endometritis (PBIE) as the third most common disease in mares is a leading reason for infertility. Some mares do not respond effectively to traditional treatments including uterine lavage, and administration of antibiotics, anti-inflammatories, and ecboic agents. This study explored the combined use of oxytocin and carbetocin with flunixin meglumine for treating PBIE in Dareh Shouri mares. The study involved 45 Dareh Shouri mares with PBIE. Treatment group1: mares were treated with oxytocin, flunixin meglumine, and uterine lavage with normal saline (15); treatment group2: mares were treated with carbetocin, flunixin meglumine, and uterine lavage with normal saline (15); and control, only uterine lavage with normal saline (15). Cytology samples were collected post-ovulation and pre-treatment to confirm endometritis. Pregnancy rates were assessed via ultrasonography 14 days post-ovulation. Results indicated a significantly higher pregnancy rate in the carbetocin-treated group (86%) and oxytocin-treated group (66%). A significant correlation was found between pregnancy outcomes and factors such as uterine edema, follicle size, and the interval between mating and ovulation. This study highlights the potential effectiveness of using oxytocin and carbetocin with flunixin meglumine for treating PBIE in Dareh Shouri mares, though further research is necessary for definitive conclusions.

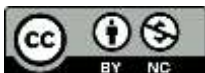
Key words: Persistent Breeding-Induced Endometritis, Carbetocin, Oxytocin, Flunixin meglumine, Dareh Shouri Mares

Introduction

Endometritis as a prevalent cause of infertility in mares has been reported to be the third health condition in the equine

species (Talebkhani Garoussi et al, 2022; Traub-Dargatz et al, 1991). Endometritis occurs when the uterus exhibits a weakened

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ability to clear microorganisms (Morris et al, 2020). Also, predisposing factors of this health disorder encompass a history of dystocia or placental retention, reproductive tract anatomical defects, and inadequate uterine clearance after natural mating or artificial insemination (AI) (Troedsson, 2006; Troedsson and Woodward, 2016). These factors contribute to a decrease in horse fertility (Bucca et al, 2008).

There are three crucial types of endometritis in mares including genital endometritis, persistent-breeding-induced endometritis (PBIE), and chronic uterine infections. Persistent-mating-induced endometritis has been introduced as the predominant form of non-infectious endometritis (Troedsson, 1999; Troedsson and Woodward, 2016). Reports suggest that approximately 10 to 15 percent of mares are susceptible to PBIE (Canisso et al, 2020; LeBlanc, 2010).

Endometritis contributes to a decline in the fertility rate in mares by creating an unsuitable uterine environment for embryos 5 to 6 days after ovulation. It is noteworthy that the occurrence of endometritis after mating is a normal phenomenon in all mares (Zent et al, 1998). However, in most mares, this inflammatory process is transient, and within 24 to 48 hours, the uterus is cleared of inflammatory substances and cells (Pycock and Allen, 1990). In contrast, this inflammation persists in sensitive mares and causes persistent-breeding induced endometritis. Several factors predispose mares to persistent-breeding induced endometritis. Aging and poor perinatal structure are the most significant contributors (Brito and Barth, 2003). Older mares are more susceptible to persistent-mating endometritis than their younger counterparts.

Treatment options for endometritis are diverse and encompass various approaches. These may involve uterine lavage using solutions such as Ringer's lactate or buffered saline, anti-inflammatory treatment, mucolytic compounds,

antibiotics and oxytocin (Christoffersen et al, 2012; Fedorka et al, 2018; MacAllister et al, 1993; Rogan et al, 2007).

Oxytocin is synthesized in the hypothalamus and stored in the posterior pituitary gland to be released in response to the related signals. Oxytocin stands out as the most widely recognized drug for enhancing uterine contraction and fluid outflow in mares (Holleboom et al, 2013; LeBLANC et al, 1994; Risco et al, 2009).

Carbetocin, a synthetic oxytocin analog, is a long-acting alternative with a half-life of around 2.5 times longer than oxytocin in horse. The half-life of oxytocin is relatively short (6.8 minutes in horse). The extended duration of action of carbetocin may offer advantages in certain therapeutic contexts compared to the transient effects of oxytocin (de Amorim et al, 2023; Holleboom et al, 2013; Schramme et al, 2008).

According to studies, repeated doses of oxytocin are employed to treat endometritis after mating. Considering the extended half-life of carbetocin and therefore, the possibility of using it as a single dose for treatment persistent-breeding induced endometritis, the present study was designed to evaluate the effect of using exogenous administration of oxytocin or carbetocin along with flunixin meglumine and uterine lavage on the treatment of persistent-breeding-induced endometritis in Dare-shuri mares.

Materials and Methods

Animals and Experimental Design

This study was conducted on 45 Dereh-Shuri mares with PBIE between the ages of 8 and 24 years, from June 2022 to November 2023. The studied mares were divided in to three groups. Treatment group 1: mares were treated with oxytocin along with flunixin meglumine and uterine lavage with 2-3 liters saline solution (15). Treatment group 2: mares were treated with carbetocin along with flunixin meglumine and uterine lavage with 2-3 liters of saline solution (15),

control: only uterine lavage with 2-3 liters saline solution. The Mean±SE time intervals between mares' parturition and entering the study were 35.6±4.99, 29.4±4.34 and 35.2±4.58 in control, treatment group 1 and treatment group 2 respectively. The Mean±SE of mares' parity was 8.13±0.46, 6.06±0.44 and 7.26±0.40 in control, treatment group 1 and treatment group 2 respectively. All mares included in this study were kept in stables that provide adequate and appropriate nutrition for the mares.

Evaluation and preparation of mares for mating or AI

Prior to the clinical trial and the commencement of the study, the mares under investigation underwent rectal ultrasound examinations (Emp V9, China) at 24-hour intervals during the estrous period to determine the precise mating time. These mares were evaluated for signs of ovulation (such as changes in follicle shape, reduction in uterine edema, and constancy of follicle size). Subsequently, 25 micrograms of Vetaroline (Aburaihan, Tehran, Iran) were administered via intramuscular injection 24 and 12 hours before mating to induce ovulation. The uterus was also evaluated by ultrasound examination. The mares showed more than 1 cm of non-echogenic fluid or any amount of echogenic fluid accumulation in the uterus during estrus, were excluded from the study. The uterine edema and follicular size were measured and recorded at the last ultrasonography before mating or insemination.

Twelve stallions were used for mating or artificial insemination in this study and all of the stallions had normal fertility based on their history. Based on the indicators of the nearness of ovulation mentioned above, the approximate time of ovulation was determined. At this point, natural mating or artificial insemination was performed using a 65 cm pipette (Mini Tube, Germany), which was inserted into the posterior part of

the uterine body. The total volume of semen inseminated to obtain normal fertility was 15-20 ml. This volume was based on the motility and concentration of sperm in the sample.

Evaluation for diagnosis of endometritis and uterine cytology preparation

Between 24 to 48 hours following mating or insemination with fresh sperm, mares underwent another ultrasound examination to confirm ovulation. In some of the studied mares and because of the field conditions, ultrasound examination for detection of ovulation was performed less than 24 hours after insemination. If ovulation was detected, uterine fluid cytology was examined to confirm the diagnosis of endometritis before initiating treatment. The cytology samples were collected from the mares that showed more than 1 cm of non-echogenic fluid or any amount of echogenic fluid accumulation in the uterus. The study continued until 45 mares with PBIE were gathered for the study.

The mares' tails were first thoroughly closed to conduct the cytology, and the vulva was meticulously cleaned with betadine scrub. Subsequently, the sample was gently collected using a sampling brush to prepare a smear. Using the index finger, sampling brush was put into the body of uterus through cervix. In the uterine body, its cap was removed by moving it forward. The brush was held in the endometrial cavity for 10 to 15 sec. The collected sample was used for smear preparation.

After fixation of smear with 95% methanol for 30 seconds, prepared smears were stained using Giemsa 10% for 20 minutes. Subsequently, all slides were rinsed with water. Following drying, the slides were examined using a light microscope with 1000x magnification and immersion oil, and interpreted as follows: between 0-2 neutrophils in each field were considered normal. Between 3-5 neutrophils in each field were deemed indicative of moderate inflammation. The

presence of >5 neutrophils in each field was indicative of severe inflammation (McKinnon et al, 2011). Fourteen days after ovulation, the mares under study underwent rectal ultrasound (Emp V9, China) examination to assess pregnancy.

Just one mating or AI was done for each mare and if the mare did not ovulate during 48 h after mating or AI, that mare was excluded from the study. Treatment procedures in all groups were done once and the result of pregnancy was evaluated and considered for the present study after this treatment. Non-pregnant mares were treated based on their uterine and ovarian condition in the next estrus cycles.

Treatment procedures for mares with PBIE

The first treatment group comprises mares subjected to uterine lavage with 2 to 3 liters saline solution, along with intramuscular injection of 20 units of oxytocin (Rooyan, Iran) and flunixin meglumine (Razak, Iran) that administered intravenously at a 1.1 mg/kg dosage, one hour after oxytocin injection and uterine lavage, and upon diagnosis of the complication (within 24 to 48 hours after mating). The second treatment group comprised mares that received uterine lavage with 2 to 3 liters saline solution, along with intramuscular injection of 0.175 mg of carbetocin (Hanlim Pharm, South Korea) and flunixin meglumine was administered intravenously at a 1.1 mg/kg dosage, one hour after the injection of carbetocin. The control group included mares that underwent uterine lavage with 2 to 3 liters saline solution at the time of diagnosis, which occurred between 24 to 48 hours after mating. All treatments were started within 24 to 48 hours after mating for all groups. Endometritis detection was done at the time of ovulation detection in this study (within 24 to 48 hours after mating).

Statistical analysis

The data were analyzed using IBM SPSS23. Categorical data were analyzed by Kruskal-Wallis Test. The correlation between data were analyzed using Spearman's correlation. The differences at the level of 5% ($P < 0.05$) were considered significant.

Results

Age of the mares

The age of the mares in this study, among the groups receiving oxytocin, carbetocin, and the control, was between 8-24 years, 14 years on average. The mares range and average of the mares are shown in Table 1. The results indicated no significant difference in the average age of mares between the groups ($P > 0.05$).

Table 1: The range and mean±SE of the age of mares in experimental groups

Groups	Range (year)	Mean±SE (year)
Oxytocin Group	11-20	13.93±2
Carbetocin Group	8-24	13.06±3
Control Group	12-22	15.92±2

Pregnancy rates in mares

In total, 32 mares breed by natural mating and 13 mares breed by AI in this study. In the control group, out of a total of 15 treated mares, 6 mares (40%) became pregnant (Figure 1). In the group receiving oxytocin, out of 15 treated mares, 10 mares (66%) became pregnant which was statistically different compared to the control group ($P < 0.05$) (Figure 1). In the group receiving carbetocin, out of 15 treated mares, 13 mares (86%) became pregnant which was different compared to the control group ($P < 0.05$) (Figure 1). The pregnancy rate of the oxytocin group was not significantly different in comparison with the carbetocin group ($P > 0.05$).

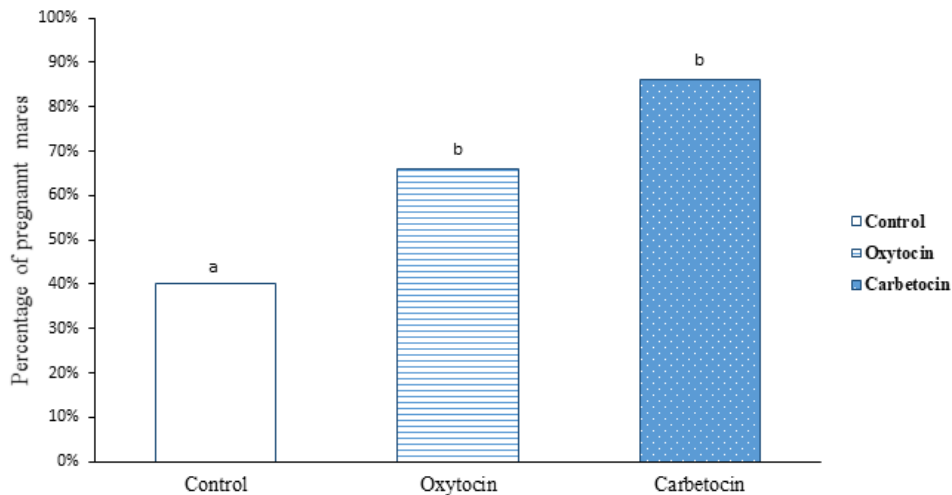


Figure 1: The pregnancy rate of mares among experimental groups. Different letters show significant differences between groups.

Uterine cytology

The results related to evaluation of uterine cytology between 24 to 48 hours following mating or insemination and immediately before treatment in the groups receiving oxytocin, carbetocin, and the control are shown in Figure 2. No significant difference in the uterine

cytology status was observed among the groups ($P>0.05$).

Uterine edema

The results of comparing uterine edema degree among the oxytocin, carbetocin, and the control groups, showed no significant difference ($P>0.05$) (Figure 3).

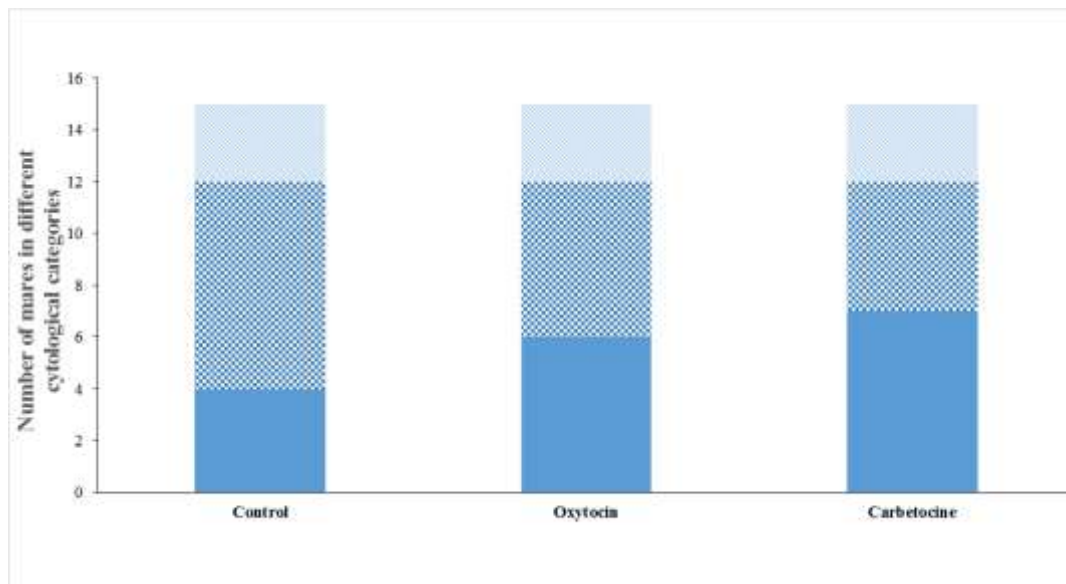


Figure 2: Frequency of mares based on cytology category among experimental groups. ■: Number of 0-2 neutrophils in 5 microscopic sections with X1000 magnification; ▨: Number of 3-5 neutrophils in 5 microscopic sections with X1000 magnification; ▩: Number of <5 neutrophils in 5 microscopic sections with X1000 magnification

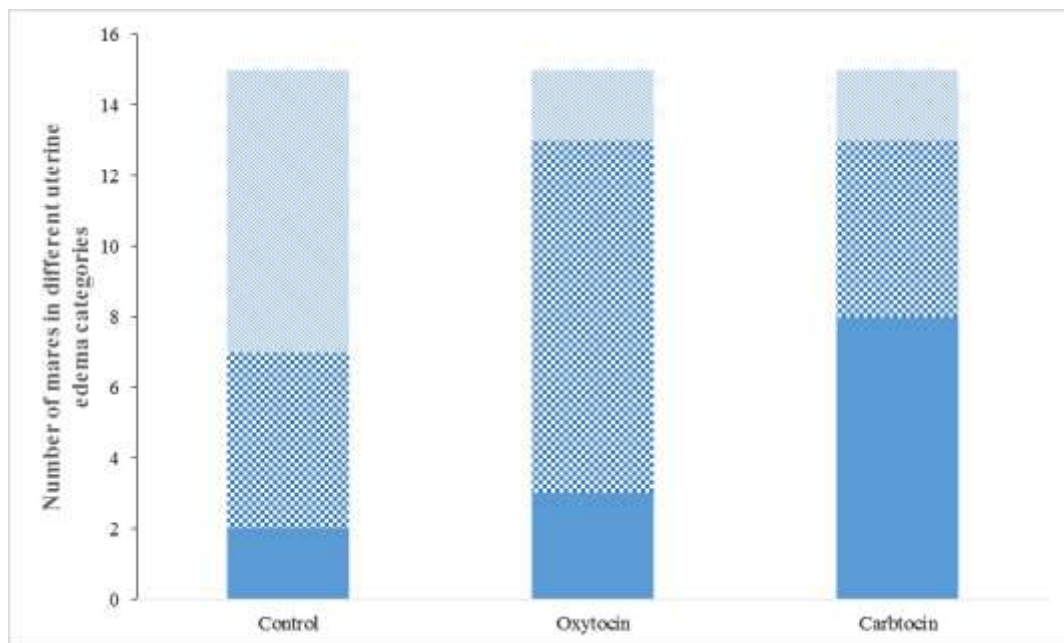


Figure 3: Frequency of mares based on uterine edema category among experimental groups. ■: edema grade 1; ▨: edema grade 2; ▩: edema grade 3.

Preovulatory follicle diameter

Preovulatory follicle diameter in the studied mares ranged from 3.9 cm to 4.5 cm, with an average of 4.4 cm. The range and average diameter of preovulation follicles in the experimental group are shown in Table 2. A statistically significant correlation was observed between pregnancy in mares with Preovulatory follicle diameter before mating ($P < 0.003$).

Table 2: The range and mean±SE of preovulatory follicle diameter of mares in experimental groups

Groups	Range (cm)	Mean±SE (cm)
Oxytocin Group	3.7-4.6	4.3±1
Carbetocin Group	3.9-5.6	4.3±2
Control Group	4.1-4.2	4.2±1.5

Mating to ovulation interval

The interval between mating to ovulation in the studied mares varied from 18 to 48 hours, with an average of 38 hours. The

range and average of the mating interval to ovulation in experimental groups are shown in Table 3. The correlation between pregnancy rate in mares and mating to ovulation interval was not significant ($P < 0.068$).

Table 3: Mating to ovulation interval in mares

Groups	Range (h)	Mean±SE (h)
Oxytocin Group	48-18	34.9±4
Carbetocin Group	48-18	36.9±3
Control Group	39-48	42±2

Correlation between evaluated variables

There were significant correlations between pregnancy and uterine cytology 48 hours after mating and immediately before treatment, pregnancy and dominant follicle size before mating and uterine cytology and dominant follicle size before mating ($P < 0.05$). The correlations between other evaluated variables were not significant ($P > 0.05$) (Table 4).

Table 4: Correlation between evaluated variables

	Pregnancy	Cytology	Uterine edema	Uterine fluid	dominant follicle size	Age	Mating to ovulation interval	GnRH injection to ovulation interval
Pregnancy	1	r= 0.603 p= 0.001	r= -0.340 p= 0.24	r= 0.103 p= 0.252	r= 0.443 p= 0.003	r= -0.038 p= 0.807	r= -0.278 p= 0.068	r= -0.018 p= 0.228
Cytology		1	r= 0.336 p= 0.14	r= -0.083 p= 0.297	r= -0.436 p= 0.003	r= 0.205 p= 0.182	-	-
Uterine edema			1	r= 0.179 p= 0.244	r= -0.219 p= 0.153	-	-	-
Uterine fluid				1	r= 0.116 p= 0.455	r= 0.27 p= 0.860	-	-
dominant follicle size					1	-	-	-
Age						1	-	-
Mating to ovulation interval							1	r= -0.185 p= 0.228
GnRH injection to ovulation interval								1

Discussion

Post-breeding-induced endometritis (PBIE) as the third common disease in adult mares accounts for the main cause of infertility, affecting approximately 15% of mares (Hurtgen, 2006; LeBlanc and Causey, 2009). Traditionally, endometritis is treated with the administration of drugs such as anti-inflammatory substances, antibiotics, and ecbolics concomitant with lavage of the uterus. Unfortunately, some mares do not respond to these treatments (Liu and Troedsson, 2008). In addition to the ecbolic agents, administration of cloprostenol can be used for uterine clearance in the mare and it is mentioned

that this prostaglandin analogue has a longer activity duration compared to oxytocin (Combs et al, 1996). However, it is shown that when this drug is administered during the periovulatory period until two days post-ovulation, it has a negative effect on progesterone levels during the early days after ovulation (Nie et al, 2003).

These treatments are sometimes not effective enough, and the prevalence of antibiotic-resistant microorganisms has increased, which necessitates the development of alternative medications for mares with persistent-breeding endometritis

(Buczowska et al, 2015; Scoggin, 2016). The present research was aimed to investigate the effect of using exogenous administration of oxytocin or carbetocin along with flunixin meglumine and uterine lavage on the persistent-breeding induced endometritis treatment in Dare-Shuri mares. The results of some studies show that oxytocin administration stimulates a pulse of PGFM (a PGF_{2a} metabolite) that mimics a natural PGFM pulse during luteolysis in mare. In the study of Santos et al, (2016), single injection of oxytocin with each of doses (1–10 IU/mare) stimulated a burst of PGFM that was maximum in 4 minutes, but this burst was unlike a natural pulse. In this study, oxytocin infusion during 2 hours with doses of 1.25, 2.5, or 5 IU/100 kg induced a PGFM pulse similar natural pulse and the peak of an induced seemed similar to reported natural peaks. Percentage decrease in progesterone within 8 hours was significantly greater for this group (oxytocin infusion during 2 hours) than saline injected group. Considering that, oxytocin injection was 1 or 2 days after ovulation in our study and to prevent possible adverse effect of oxytocin on CI development and progesterone concentration, only one injection of oxytocin was considered in this study. In the study by Rasch et al., the effect of oxytocin on the rate of uterine clearance and pregnancy in mares showed that intravenous oxytocin administration in mares suffering from the accumulation of intrauterine fluid increased fertility (Rasch et al, 1996). According to Guthjahr et al, oxytocin treatment should begin in the preovulatory period because the response of the uterus to oxytocin is greater when progesterone levels are low and estrogen levels are high. If oxytocin treatment is used after ovulation, the dose should be increased to achieve a better effect. However, caution is necessary, as administering more than 25 IU of oxytocin can cause persistent contractions, spasms, and tetany, leading to uterine fluid retention

(Guthjahr et al, 2000). In the present study, the pregnancy rates in mares of the control and oxytocin groups were 40%, and 66% respectively, which was significantly different between the oxytocin-treated and the control groups. Therefore, according to the obtained results, oxytocin increases the pregnancy rate in mares.

Carbetocin, with a half-life of 17.2 minutes, can be used in mares as an alternative to oxytocin, which has a half-life of 6.8 minutes (Schramme et al, 2008). One of the disadvantages of oxytocin is the need for repeated doses, making carbetocin more practical. However, to date and to the extent that the authors have investigated, no studies have compared the effect of oxytocin and carbetocin to accelerate uterine clearance (de Amorim et al, 2023; Steckler et al, 2012). In the present study, the pregnancy rate examined in mares was 40% in the control group compared to 86% in carbetocin group. A significant difference was observed between the carbetocin group and the control group. In the study by Khan et al., preovulatory administration of ecbolics in mares resistant to endometrial infection did not affect the clearance of the uterus or luteal development. Moreover, carbetocin did not have the expected effect on uterine clearance but this treatment had no side effect on the corpus luteum until day 14. Therefore, pre- and post- ovulation treatment with carbetocin, twice-daily, is safe in inseminated mares (Khan et al, 2024).

In this study, flunixin meglumine was used in treatment groups alongside oxytocin and carbetocin. In the study by Donnelly et al., the administration of flunixin meglumine did not affect the time interval between the detection of a follicle ≥ 30 mm to ovulation. The pregnancy rate per cycle was not significantly different in flunixin meglumine-treated (83% of matings) compared to the control group (68% of matings). Flunixin meglumine had no significant effect on the behavioral symptoms of estrus, uterine edema, or

serum progesterone concentration (Donnelly et al, 2019).

In our study, there was no significant difference in cytology grade, among the groups that received oxytocin or carbetocin or no treatment, at 48 hours after mating and immediately before treatment. In the study by Riddle et al. (2007), the pregnancy rate of mares with positive cytology or bacterial culture was lower than those with negative culture ($P < 0.01$). The mares with severe endometrial inflammation had a lower pregnancy rate than those with moderate inflammation (21% vs 48%). In this study, uterine cytology was used to confirm endometritis in all studied mares, and the lack of a significant difference in the present study indicates similar conditions of the studied mares, consistent with other studies.

On the other hand, to create uniform conditions and reduce the impact of physiological factors on fertility, a statistical comparison was made for the age of the different groups. The results of this comparison showed no significant difference in age among the groups receiving oxytocin, carbetocin, and the control. Nazem et al, (2023), reported a significant difference in the age of mares with endometritis after mating. The absence of significant difference in age between the groups in our study helped to clarify the effect of treatments among groups.

To ensure the uniformity of study conditions in mares, the average diameter of the follicles before ovulation and the average mating interval until ovulation was investigated across different groups. No statistically significant difference was observed. These results are important in confirming the presence of the normal estrus cycle and similar physiological conditions among the mares.

The results for uterine edema in mares receiving oxytocin, carbetocin, and the control showed no statistically significant difference. Inflammatory changes in the uterus of mares are typically indicated by the presence of uterine fluid or a significant

increase in endometrial edema. During the normal estrous cycle, endometrial edema is used as a diagnostic factor and correlates with estrogen production. Typically, the degree of edema near ovulation is low or absent. When edema is detected in mares that are in diestrus or pregnant, it is a sign of inflammation. In the present study, there was a direct but not significant correlation between pregnancy in mares and uterine edema before mating (Del Prete, Montano, et al, 2024; Del Prete, Nocera, et al, 2024).

Mateu-Sánchez et al, reported that the pregnancy rate was positively correlated with the duration of estrus and endometrial edema in both natural and prostaglandin-induced cycles. Additionally, a positive and significant correlation was found between the length of endometrial edema and both the interval between ovulation and the interval from PG treatment to ovulation (Mateu-Sánchez et al, 2016). In the study by Grabowska and Kozdrowski, there was a significant relationship between the level of progesterone at 14 days post ovulation and the presence of endometrial edema observed at estrus. Sometimes, lack of sufficient endometrial edema at estrus has been related to low progesterone concentration 14 days post-ovulation (Grabowska and Kozdrowski, 2022).

Upon our results, a positive and significant correlation was detected between pregnancy and the size of the dominant follicle before mating. The diameter and growth rate of the follicle before ovulation at the beginning of estrus can affect the duration of estrus until ovulation in mares. It has been demonstrated that the size of the dominant follicle significantly affects the intensity of estrus in mares (Grabowska and Kozdrowski, 2022).

The results of the present study support the effectiveness of using a combination of flunixin meglumine and carbetocin to treat persistent-mating endometritis in mares. Considering that, carbetocin has a longer duration of action than oxytocin and does

not have the side effects mentioned in previous the studies, it is probably a suitable option for persistent-breeding-induced endometritis treatment in mares. However, more studies especially on more severe or

complicated endometritis cases which do not respond to routine oxytocin treatments, probably may indicate the advantages of using carbetocin in treatment of endometritis in mares.

Acknowledgements

The authors thank Shahrekord University for funding of this research. The authors wish to give thanks to the breeders that helped and supported us in conducting research and sample collection.

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding

This study was funded by Shahrekord University.

Reference

- Brito, L., & Barth, A. (2003). Endometritis in mares. *Large Animal Veterinary Rounds*, 3(9).
- Bucca, S., Carli, A., Buckley, T., Dolci, G., & Fogarty, U. (2008). The use of dexamethasone administered to mares at breeding time in the modulation of persistent mating induced endometritis. *Theriogenology*, 70(7), 1093-1100.
- Buczowska, J., Kozdrowski, R., Sikora, M., Dzięcioł, M., & Matusz, A. (2015). Non-traditional treatments for endometritis in mares. *Bulgarian Journal of Veterinary Medicine*, 18(4).
- Canisso, I. F., Segabinazzi, L. G., & Fedorka, C. E. (2020). Persistent breeding-induced endometritis in mares—A multifaceted challenge: From clinical aspects to immunopathogenesis and pathobiology. *International journal of molecular sciences*, 21(4), 1432.
- Christoffersen, M., Woodward, E., Bojesen, A., Petersen, M., Squires, E., Lehn-Jensen, H., & Troedsson, M. (2012). Effect of immunomodulatory therapy on the endometrial inflammatory response to induced infectious endometritis in susceptible mares. *Theriogenology*, 78(5), 991-1004.
- Combs, G.B., LeBlanc, M.M., Neuwirth, L., Tran, T.Q. (1996). Effects of prostaglandin F2 [alpha], cloprostenol and fenprostalene on uterine clearance of radiocolloid in the mare. *Theriogenology*, 45, 1449-1455.
- de Amorim, M. D., Bramer, S. A., Rajamanickam, G. D., Klein, C., & Card, C. (2023). Serum progesterone and oxytocinase, and endometrial and luteal gene expression in pregnant, nonpregnant, oxytocin, carbetocin and meclofenamic acid treated mares. *Theriogenology*, 198, 47-60.
- Del Prete, C., Montano, C., Cocchia, N., de Chiara, M., Gasparrini, B., & Pasolini, M. P. (2024). Use of regenerative medicine in the treatment of endometritis in mares: a systematic review and meta-analysis. *Theriogenology*.
- Del Prete, C., Nocera, F. P., Piegari, G., Palumbo, V., De Martino, L., Cocchia, N., Paciello, O., Montano, C., & Pasolini, M. P. (2024). Use of cytobrush for bacteriological and cytological diagnosis of endometritis in mares. *Veterinary World*, 17(2), 398.
- Donnelly, C. G., Sones, J. L., Dockweiler, J. C., Norberg, L. A., Norberg, L. E., Cheong, S. H., & Gilbert, R. O. (2019). Effects of flunixin meglumine on postponement of ovulation in mares. *American journal of veterinary research*, 80(3), 306-310.
- Fedorka, C., Scoggin, K., Boakari, Y., Hoppe, N., Squires, E., Ball, B., & Troedsson, M. (2018). The anti-inflammatory effect of exogenous lactoferrin on breeding-induced endometritis when administered post-breeding in susceptible mares. *Theriogenology*, 114, 63-69.
- Grabowska, A., & Kozdrowski, R. (2022). Relationship between estrus endometrial edema and progesterone production in pregnant mares two weeks after ovulation. *BMC Veterinary Research*, 18(1), 414.

- Gutjahr, S., Paccamonti, D., Pycock, J., Taverne, M., Dieleman, S., & Van der Weijden, G. (2000). Effect of dose and day of treatment on uterine response to oxytocin in mares. *Theriogenology*, 54(3), 447-456.
- Holleboom, C., Van Eyck, J., Koenen, S., Kreuwel, I., Bergwerff, F., Creutzberg, E., & Bruinse, H. (2013). Carbetocin in comparison with oxytocin in several dosing regimens for the prevention of uterine atony after elective caesarean section in the Netherlands. *Archives of gynecology and obstetrics*, 287, 1111-1117.
- Hurtgen, J. P. (2006). Pathogenesis and treatment of endometritis in the mare: a review. *Theriogenology*, 66(3), 560-566.
- Khan, Y., El-Shalofy, A., Kaps, M., Gautier, C., & Aurich, C. (2024). In mares resistant to endometrial infection, periovulatory treatment with ecbolic drugs does not influence uterine clearance or luteal development. *Animal Reproduction Science*, 107548.
- LeBlanc, M. (2010). Advances in the Diagnosis and Treatment of Chronic Infectious and Post-Mating-Induced Endometritis in the Mare. *Reproduction in domestic animals*, 45, 21-27.
- LeBlanc, M., & Causey, R. (2009). Clinical and subclinical endometritis in the mare: both threats to fertility. *Reproduction in Domestic Animals*, 44, 10-22.
- LeBLANC, M., Neuwirth, L., Mauragis, D., Klapstein, E., & Tran, T. (1994). Oxytocin enhances clearance of radiocolloid from the uterine lumen of reproductively normal mares and mares susceptible to endometritis. *Equine veterinary journal*, 26(4), 279-282.
- Liu, I., & Troedsson, M. (2008). The diagnosis and treatment of endometritis in the mare: Yesterday and today. *Theriogenology*, 70(3), 415-420.
- MacAllister, C. G., Morgan, S. J., Borne, A. T., & Pollet, R. A. (1993). Comparison of adverse effects of phenylbutazone, flunixin meglumine, and ketoprofen in horses. *Journal of the American Veterinary Medical Association*, 202(1), 71-77.
- Mateu-Sánchez, S., Newcombe, J., Garcés-Narro, C., & Cuervo-Arango, J. (2016). The period of the follicular phase during which the uterus of mares shows estrus-like echotexture influences the subsequent pregnancy rate. *Theriogenology*, 86(6), 1506-1515.
- McKinnon, A. O., Squires, E. L., Vaala, W. E., & Varner, D. D. (2011). *Equine reproduction*. John Wiley & Sons.
- Morris, L. H., McCue, P., & Aurich, C. (2020). Equine endometritis: A review of challenges and new approaches. *Reproduction*, 160(5), R95-R110.
- Nazem, Y., Shams Esfandabadi, N., Kadivar, A., Davoodian, N., & Nazari, H. (2023). Evaluation the prevalence of persistent post-mating endometritis in Arabian mares. *Iranian Journal of Veterinary Clinical Sciences*, 17(1), 71-79.
- Nie, G.J., Johnson, K.E., Wenzel, J.G., Braden, T.D. (2003). Effect of administering oxytocin or cloprostenol in the periovulatory period on pregnancy outcome and luteal function in mares. *Theriogenology*, 60: 1111-1118.
- Pycock, J., & Allen, W. (1990). Inflammatory components in uterine fluid from mares with experimentally induced bacterial endometritis. *Equine veterinary journal*, 22(6), 422-425.
- Rasch, K., Schoon, H., Sieme, H., & Klug, E. (1996). Histomorphological endometrial status and influence of oxytocin on the uterine drainage and pregnancy rate in mares. *Equine veterinary journal*, 28(6), 455-460.
- Riddle, W., LeBlanc, M., & Stromberg, A. (2007). Relationships between uterine culture, cytology and pregnancy rates in a Thoroughbred practice. *Theriogenology*, 68(3), 395-402.
- Risco, A., Reilas, T., Muilu, L., Kareskoski, M., & Katila, T. (2009). Effect of oxytocin and flunixin meglumine on uterine response to insemination in mares. *Theriogenology*, 72(9), 1195-1201.
- Rogan, D., Fumuso, E., Rodriguez, E., Wade, J., & Bruni, S. S. (2007). Use of a mycobacterial cell wall extract (MCWE) in susceptible mares to clear experimentally induced endometritis with *Streptococcus zooepidemicus*. *Journal of Equine Veterinary Science*, 27(3), 112-117.
- Santos, V.G., Castro, T., Bettencourt, E.M., & Ginther O.J. . (2015). Oxytocin induction of pulses of a prostaglandin metabolite and luteolysis in mares. *Theriogenology*, 83, 730-738.
- Schramme, A., Pinto, C., Davis, J., Whisnant, C., & Whitacre, M. (2008). Pharmacokinetics of carbetocin, a long-acting oxytocin analogue, following intravenous administration in horses. *Equine veterinary journal*, 40(7), 658-661.
- Scoggin, C. F. (2016). Endometritis: nontraditional therapies. *Veterinary Clinics: Equine Practice*, 32(3), 499-511.
- Steckler, D., Naidoo, V., Gerber, D., & Kähn, W. (2012). Ex vivo influence of carbetocin on equine myometrial muscles and comparison with oxytocin. *Theriogenology*, 78(3), 502-509.

- Talebkhan Garoussi, M., Soleymani, M., Salehi Zahraei, T., & Gharagozloo, F. (2023). The survey of *Pseudomonas aeruginosa* infection of reproduction system of mares in both Suburb of Tehran and Alborz provinces of Iran. *Iranian Veterinary Journal*, 18(4), 59-66.
- Traub-Dargatz, J., Salman, M., & Voss, J. (1991). Medical problems of adult horses, as ranked by equine practitioners. *Journal of the American Veterinary Medical Association*, 198(10), 1745-1747.
- Troedsson, M. (1999). Uterine clearance and resistance to persistent endometritis in the mare. *Theriogenology*, 52(3), 461-471.
- Troedsson, M. H. (2006). Breeding-induced endometritis in mares. *Veterinary Clinics: Equine Practice*, 22(3), 705-712.
- Troedsson, M. H., & Woodward, E. M. (2016). Our current understanding of the pathophysiology of equine endometritis with an emphasis on breeding-induced endometritis. *Reproductive biology*, 16(1), 8-12.
- Zent, W. W., Troedsson, M. H., & Xue, J.-L. (1998). Postbreeding uterine fluid accumulation in a normal population of Thoroughbred mares: a field study. *Proc Am Assoc Equine Pract*, 44, 64-65.

Received: 02.10.2024

Accepted: 21.11.2024

ارزیابی اثر اکسی‌توسین یا کاربتوسین همراه با تجویز فلونیکسین مگلو مین و شستشوی رحم بر درمان اندومتريت پایدار پس از جفت گیری در مادیا نهای دره شوری

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تاریخ پذیرش: ۱۴۰۳/۹/۱

تاریخ دریافت: ۱۴۰۳/۷/۱۱

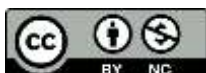
چکیده

اندومتريت پایدار پس از جفت گیری (PBIE) سومین بیماری شایع و یکی از علل اصلی ناباروری در مادیا نهای است. برخی از مادیا نهای به درمان‌های رایج شامل شستشوی رحم، آنتی‌بیوتیک‌ها، ضدالتهاب‌ها و عوامل انقباض دهنده رحم به طور موثر پاسخ نمی‌دهند. اما این مطالعه کاربرد ترکیبی اکسی‌توسین و کربیتوسین به همراه فلونیکسین مگلو مین برای درمان PBIE در مادیا نهای دره شوری را مورد بررسی قرار داد. این مطالعه شامل ۴۵ مادیا نهای دره شوری مبتلا به PBIE بود. گروه درمانی ۱: درمان با اکسی‌توسین، فلونیکسین مگلو مین و شستشوی رحم با نرمال سالین انجام شد (۱۵ رأس مادیا نهای). گروه درمانی ۲: درمان با کاربتوسین، فلونیکسین مگلو مین و شستشوی رحم با نرمال سالین انجام شد (۱۵ رأس مادیا نهای). کنترل: فقط شستشوی رحم با نرمال سالین انجام شد (۱۵ رأس مادیا نهای). نمونه‌های سیتولوژی پس از تخمک گذاری و قبل از درمان برای تأیید آندومتريت جمع‌آوری شد. میزان بارداری ۱۴ روز پس از تخمک گذاری از طریق سونوگرافی ارزیابی شد. نتایج نشان داد که میزان بارداری به طور معنی‌داری در گروه تحت درمان با کاربتوسین (۸۶ درصد) و گروه تحت درمان با اکسی‌توسین (۶۶ درصد) بالا بود. ارتباط معنی‌داری بین آبستنی و عواملی مانند ادم رحم، اندازه فولیکول و فاصله بین جفت گیری تا تخمک گذاری مشاهده شد. این مطالعه اثر بخشی بالقوه استفاده از اکسی‌توسین و کربیتوسین با فلونیکسین مگلو مین را برای درمان PBIE در مادیا نهای دره شوری نشان می‌دهد، اگرچه تحقیقات بیشتر برای نتیجه‌گیری قطعی ضروری است.

کلمات کلیدی: اندومتريت القا شده پس از جفت گیری، کربیتوسین، اکسی‌توسین، فلونیکسین مگلو مین، مادیا نهای دره شوری

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