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The effect of atonic uterus treatment on metritis, reproduction, removal, and milk yield in Holstein cows

Účinok liečby atónie maternice na metritídou, reprodukciou, vyraďovanie a mliečnu produkciu holštajnských dojníc

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ABSTRACT

The study aimed to determine the effects of medical treatment of postpartum uterus pathologies on uterine health, and the reproductive and productive performance of dairy cows during the lactation period. In total, 206 cows were examined to monitor the uterus involution process at 1, 7, 14, and 21 days in milk (DIM). Cows with retained placenta were treated with carbetocin and cows with uterus atony were treated with $PGF_{2\alpha}$. Cows with puerperal metritis received ceftiofur hydrochloride. All of the dairy cows with proven uterine health were then enrolled in a synchronization protocol with artificial insemination. Intercalving interval, service period, insemination index, milk yield per lactation (kg), average milk protein and fat per lactation, parity (heifers/cows), and culling rate were analyzed. The statistical analysis revealed only a weak trend (P = 0.07) of association between the retained placenta and the inter-calving interval. The odds of having a decrease in daily milk yield in cows without metritis were 0.92 (95% CI: 0.85, 0.99) times the odds of cows with metritis. Thus, the metritis was associated with a reduction (P < 0.05) in milk yield of 0.92 kg/cow per day and a total of 281 kg in the 305 days of lactation. Reproductive and productive variables like service period, insemination index, milk protein and fat, and culling rate were not associated with uterus disorders. In conclusion, intensive monitoring and care of the reproduction health of dairy cows early after calving can decrease the risk of economic losses.

Keywords: uterus health, metritis, reproduction, milk yield, dairy cows

ABSTRAKT

Cieľom štúdie bolo zistiť vplyv liečby dojníc s diagnostikovanou patológiou maternice na následný zdravotný stav maternice, ako aj ich reprodukčnú a produkčnú výkonnosť v porovnaní s dojnicami bez abnormalít maternice. Maternice 206 dojníc boli vyšetrované 1, 7, 14 a 21 dní po otelení. Kravy so zadržaným lôžkom boli liečené karbetocínom a pri atónii maternice bol nasadený $PGF_{2\alpha}$. Dojnice s puerperálnou metritídou boli liečené hydrochloridom ceftiofuru. Všetky dojnice so zdravou maternicou boli potom zaradené do synchronizačného protokolu s umelou insemináciou. Následne sa pre analýzu zaznamenávali reprodukčné a produkčné ukazovatele: interval, servis perióda, inseminačný index, dojivosť za laktáciu (kg), priemerná mliečna bielkovina a tuk za laktáciu, parita (jalovice/kravy) a brakovanie. Štatistická analýza odhalila len slabý trend (P = 0,07) súvislosti medzi zadržanou placentou a medziobdobím. Šanca na pokles dennej dojivosti pri dojniciach bez metritídy bola 0,92 (95 % CI: 0,85, 0,99) krát vyššia ako pri dojniciach s metritídou. Metritída teda súvisela so znížením (P < 0,05) dennej dojivosti o 0,92 kg/dojnicu a celkovo o 281 kg za 305 dní laktácie. Reprodukčné a produkčné premenné, ako sú servis perióda, inseminačný index, mliečne bielkoviny a tuk a brakovanie, neboli spojené s poruchami maternice. Záverom možno konštatovať, že intenzívne sledovanie a starostlivosť o reprodukčný zdravotný stav dojníc po otelení môže znížiť riziko ekonomických strát.

Keywords: zdravie maternice, metritída, reprodukcia, produkcia mlieka, dojnice

INTRODUCTION

During the bovine puerperal stage, the involution of the uterus has an important role in a becoming pregnant again. During involution, besides the morphological changes of the endometrium, the size of the uterus also markedly decreases. The greatest size reduction in normal cows occurs during the first few days after parturition (Gier and Marion, 1968). After 40 days the uterus has been returned to its non-pregnant size (Okana and Tomizuka, 1987). The contractions facilitate the discharge of placental remnants and fluid to reduce the size of the uterus physically, but inefficient expulsion of the contents predisposes the uterus to contamination with opportunistic pathogens that can prolong the process of involution (Fonseca et al., 1983).

Retained placenta in cows represents a serious health problem that occurs in the last (third) phase of parturition (Laven and Peters, 1996). The retaine placenta has a decisive role in the development of metritis (Kaneene, 1995). The postpartum uterus involution should be an aseptic process, but parturition itself, disintegration of uterine caruncles and uterine lochia are very good conditions for uterus contamination and pathogen multiplication, notably in the case of immunosuppressive animals (Cai et al., 1994). The impaired immune function in the periparturient period contributes to increased susceptibility of the cow to infectious diseases at the time of calving (Kimura et al., 1999). Uterine involution is usually delayed in case of bacterial infection (Usmani et al.,2001).

Treatment protocols, in which uterotonic drugs are administered during the puerperal phase in cows to evacuate the uterus by increasing its contractility, aim to accelerate the process of involution. Natural prostaglandin $F_{2\alpha}$ including its synthetic analogues (Eiler et al., 1984; Sobiraj et.al., 2006) and oxytocin (Eiler et al., 1984; Burton et al., 1990) are the most used drugs to accelerate the uterus involution. An alternative way to produce a prolonged uterotonic effect is to use oxytocin analogues with a longer biological activity, such as carbetocin (Sobiraj et. al., 2006) which had a prolonged uterotonic activity in cows (Bernhard et al., 1993).

The transition period, the most critical physiological stage in dairy cattle, starts 3 weeks before parturition and finishes 3 weeks thereafter. Major changes in metabolism, immune, and endocrine system are typical for this period (Kuhla, 2020). All of them can contribute to impairment of uterine protection function resulting in frequent uterine inflammation and infertility after calving (Sheldon and Dobson, 2004). The intrauterine bacterial infection causes inflammation, histological lesions of the endometrium, delays uterine involution and perturbs embryo survival (Sheldon et al., 2003). In addition, uterine bacterial infection, bacterial products or the associated inflammation, suppress pituitary LH secretion, and perturbs postpartum ovarian follicular growth and function, which disrupts ovulation in cattle (Opsomer et al., 2000; Sheldon et al., 2002). Metritis is a polymicrobial disease associated with inflammation of multiple layers of the uterine lining that affects 20 to 40% of dairy cows within the first 21 days postpartum (Sheldon et al., 2009; Jeon et al., 2015). Metritis reduces herd profitability due to decreased milk production and reproductive efficiency and increased risk of early culling (Dubuc et al., 2011; de Oliviera et al., 2020). The estimated cost of metritis includes among others therapeutic antimicrobial treatment, discarded milk, decreased milk yield, and decreased reproductive efficiency (Lima et al., 2019). In dairy herds, ceftiofur is the antibiotic of the first choice for the treatment of metritis because it is effective and it does not incur milk withdrawal (Chenault et al., 2004; McLaughlin et al., 2012).

Our objectives were to determine the effects of medical treatment of postpartum uterus pathologies on uterine health and reproductive and productive performance of dairy cows during the lactation period.

MATERIAL AND METHODS

Animals, housing, and management

This experiment was conducted from January 2020 to December 2021 in one commercial dairy herd with approximately 700 Holstein cows in Central Slovakia. During the experiment, the rolling herd average milk yield was 11,338 kg/cow. Nulliparous and parous animals were housed in free-stall pens with a deep straw bedding during the last 4 weeks of prepartum and were moved to free-stall with biogas solid digestate bedding after calving, where they were housed together.

The cows were fed a TMR diet that met or exceeded the requirements of Holstein cows producing 40 kg/d of 3.5% fat-corrected milk. During the first 21 days postpartum, the main ingredients of the diets were maize silage, haylage, concentrate (maize, soybean, rapeseed), fat supplement, enzyme blend, minerals, and molasses. Cows were milked three times per day.

Experimental design, treatments, and cure definition

In total, 206 cows were examined with rectum palpation of the uterus and its contents to monitor the involution process at 1, 7, 14, and 21 DIM. Retained placenta (RP) was diagnosed when fetal membranes failed to be completely expelled from the birth canal within 12 h of parturition. Cows with uterus atony (UA) were defined as those with flaccid and large uterus without an inflammatory discharge at 7 DIM. Cows with puerperal metritis had an enlarged and flaccid uterus with a foul-smelling uterine discharge. Cows with puerperal metritis received ceftiofur hydrochloride (1 mg/kg of BW s.c.) for five days. Uterine discharge was re-evaluated in cows diagnosed with metritis on day 10 and failure of clinical cure in cows diagnosed with metritis was defined as vaginal discharge persisted. Cows with RP were treated with carbetocin (0.35 mg per cow) for three consecutive days and cows with uterus atony (UA) were treated with $PGF_{2\alpha}$ (25 mg per cow), they received two doses with 48 hours' intervals between each dose. The cure of uterus pathologies was defined as absence of abnormal morphology and discharge on day 21. Cows developing clinical endometritis were excluded from the study.

Reproductive management, reproductive performance, and milk yield

In the farm, all of the dairy cows with proved uterine health were then enrolled in a synchronization protocol (2 injections of $PGF_{2\alpha}$, 14 d apart) starting on 39±4 DIM. Once per day, a list of cows determined either by the accelerometer system (Heatime) or personal oestrus detection by observation was generated, and cows appearing on the list were artificially inseminated (AI). The cows without oestrus detection were enrolled in the Ovsynch protocol (GnRH 65 ± 3 DIM, 7 d later $PGF_{2\alpha}$, 56-72 h later GnRH and fixed-time AI at 75 ± 3 DIM). After the first postpartum AI, cows were reinseminated when Heatime or farm personnel detected a new oestrus. Pregnancy diagnosis for the evaluation of P/AI and pregnancy loss was performed by the herd veterinarian 32 and 65 days after AI using transrectal ultrasonography (Kaixin KX5200 6.5 MHz digital). In case of no pregnancy the cows were injected either by $PGF_{2\alpha}$ (functional corpus luteum) or GnRH (Ovsynch) and inseminated after oestrus detection.

Data regarding reproductive and productive outcomes were recorded. They included inter-calving interval, service period, insemination index, milk yield per lactation (kg), average milk protein and fat per lactation, parity (heifers/cows), and culling rate.

Statistical analyses

Data were analysed using R software version 3.6.3 (R Core Team, 2021). Outcomes which did not have normal distribution of the residuals (daily milk yield, milk protein, inter-calving interval, service period, insemination index, and DIM) were log-transformed, but data were back-transformed for the final presentation. For all statistical analyses, the association between independent variables and outcomes of interest was assessed initially using univariable models. All independent variables with $P \leq 0.10$ in univariable analyses were included in each multivariable model. Independent variables were removed from multivariable models using a backward stepwise elimination method if $P > 0.10$ (i.e., sequentially from the largest to smallest P-value), with the exception of metritis records that were forced into all final models. Type of parity was categorized as heifer (<2) or cow (>2). Binary responses were analysed by logistic regression. Initial models for the analyses of risk factors associated with failure of early postpartum uterus treatment to prevent metritis included the fixed effects of parity, RFM, therapy, and milk yield. Initial models for the analyses of metritis and reproductive and productive outcomes included the fixed effects of parity, inter-calving interval, insemination index, service period, milk yield and composition, and removal from the herd (i.e., died or culled).

Results were reported as odds ratios (univariable model) and adjusted odds ratios (multivariable models) followed by a 95% confidence interval (CI). Statistical significance was declared at $P \leq 0.05$, and a tendency was declared at $0.05 < P \leq 0.10$.

RESULTS

The analysis included 206 dairy cows; descriptive data regarding herd, production, and reproduction results are mentioned in Table 1. Descriptive data regarding the incidence of post-calving uterus disorders are shown in Table 2. Among them, uterus atony and metritis were the most frequent with 43.7% and 30.6%, respectively. Primiparous cows had lower rate of retained placenta and a higher proportion of metritis than multiparous cows ($P < 0.05$; Table 3).

Among 63 dairy cows diagnosed with metritis that were enrolled in this study, 15 (23.8%) failed to achieve a clinical cure by day 10.

The final models evaluating the association between uterus disorders and cow-related factors with the odds are presented in Table 4.

Table 2. Incidence of uterus disorders in early lactation of 206 Holstein cows

Disorder	Number	%
Retained placenta (RP)	28	13.6
Uterus atony (UA)	90	43.7
Metritis	63	30.6
RP and Metritis	17	8.25
UA and Metritis	62	30.1
RP and UA	22	10.7
RP and UA and Metritis	17	8.25
No disorder	109	52.9

The odds of having retained placenta for primiparous cows were 0.40 (95% CI: 0.14, 1.00) times the odds of multiparous cows having retained placenta. The odds of having atonic uterus for cows with retained placenta were 5.93 (95% CI: 2.41, 16.9) times the odds of cows without atonic uterus having retained placenta. The analysis revealed only a weak trend ($P = 0.07$) of association between the retained placenta and inter-calving interval. The logistic regression analysis showed the puerperal metritis was associated with the highest number of factors. The odds of having metritis for cows with uterus atony and primiparous cows were 297 (95% CI: 56; 5,599) and 4.54 (95% CI: 1.59, 14.2) times the

Table 1. Descriptive statistics of cow reproduction and production variables in the dataset from 206 dairy cows

Variable	Mean (Median)	SD (Range)	Missing values (no.)
Lactation	2.11	1.17	0
Days in Milk	363 (334)	80.6 (215–771)	0
Inter-calving interval (d)	389	116	0
Service period (d)	142	72.1	0
Insemination Index	3.11	2.19	0
Milk, kg/day	34.8	6.51	0
Protein (%)	3.34	0.22	0
Fat (%)	3.74	0.43	0

This dataset was to determine the effects of treating cows diagnosed with uterus pathologies on uterine health, reproductive and productive performances

Table 3. Parity proportions of single uterus disorders in 206 Holstein cows

Disorder	Primiparous (n = 83)	Multiparous (n = 123)	X^2
Retained placenta	6 (7.23%)	22 (17.9%)	*P* < 0.05
Uterus atony	42 (50.6%)	48 (39.0%)	NS
Metritis	36 (43.4%)	27 (22.0%)	*P* < 0.05
Culled by 300 DIM	5 (6.02%)	9 (7.32%)	NS

NS – not significant

Table 4. Association between uterus disorders and production, and reproduction performance in 206 Holstein cows (Final logistic regression model)

Outcome and Variable	Coefficient (SE)	Odds ratio (95% CI)	*P*-value
Retained placenta	Referent		
Intercept	-7.78 (3.93)		<0.05
Primiparous	-0.91 (0.49)	0.40 (0.14–1.00)	0.06
Milk protein (%)	1.50 (0.91)	4.48 (0.72–27.4)	0.10
Uterus atony	Referent		
Intercept	-1.48 (0.58)		<0.05
Retained placenta	1.78 (0.49)	5.93 (2.41–16.9)	<0.05
Inter-calving	0.003 (0.002)	1.00 (0.99–1.01)	0.07
Metritis	Referent		
Intercept	-3.76 (1.96)		0.05
Uterus atony	5.69 (1.07)	297 (56–5599)	<0.05
Primiparous	1.51 (0.55)	4.54 (1.59–14.2)	<0.05
Milk kg/day	-0.08 (0.04)	0.92 (0.85¬–0.99)	<0.05
Retained placenta	1.25 (0.64)	3.51 (1.05–13.4)	0.05
Inter-calving	0.002 (0.002)	1.00 (0.99–1.01)	0.41

odds of cows without atonic uterus and primiparous cows having metritis, respectively. The milk yield had a negative association with the metritis, i.e. that the less cows tended to have lower milk production, the more likely they had metritis and vice versa: the higher amount of milk cows produced, the less likely they had metritis.

The odds of having a decrease in daily milk yield in cows without metritis were 0.92 (95% CI: 0.85, 0.99) times the odds of cows with metritis. Thus, the metritis was associated with a reduction (*P* < 0.05) in milk yield of 0.92 kg/cow per day (Figure 1) and a total of 281 kg in the 305 days of lactation.

Reproductive and productive variables like service period, insemination index, milk protein and fat, and culling rate were not associated with uterus disorders.

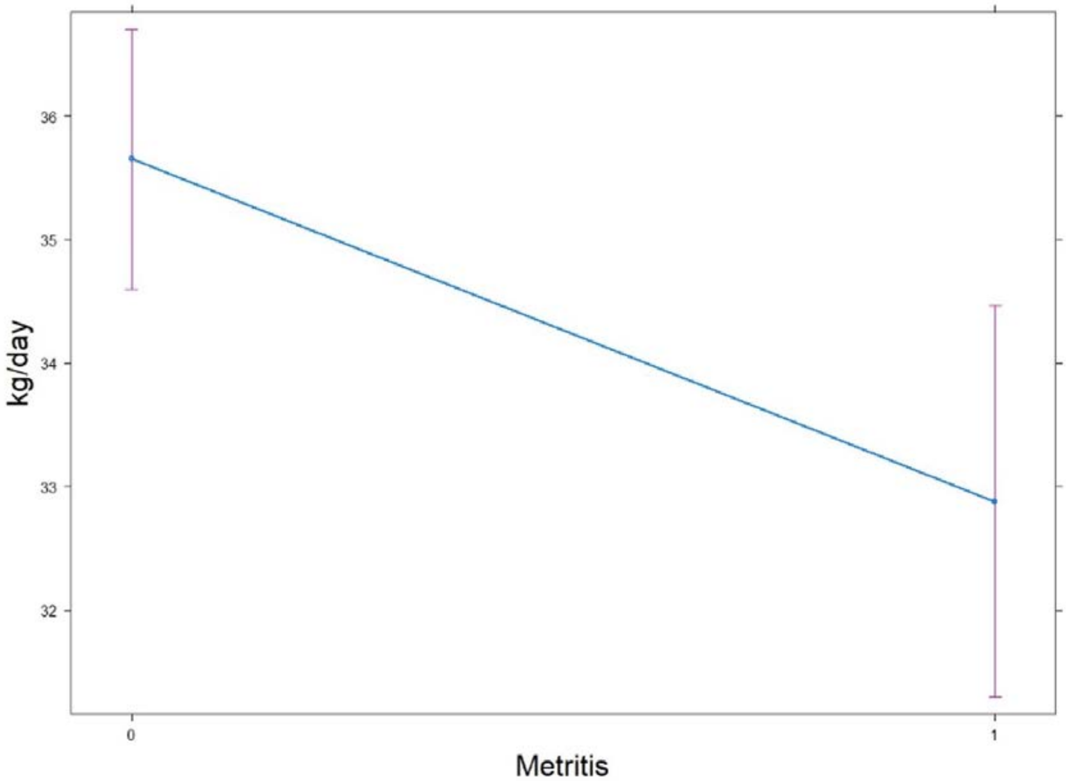

Figure 1. The association between metritis and milk yield (kg/day)

DISCUSSION

The aim of the research was to study the association of atonic uterus treatment with metritis rate, reproduction performance, removal, and milk yield in Holstein dairy cows. The observed prevalence of metritis in this herd was within the range of reported data (Giuliodori et al., 2013; Rodríguez et al., 2017). Metritis is an important herd health disorder in postpartum dairy cows that can affect 5 to 20% of cows on a farm (LeBlanc, 2014). Currently, the diagnostic criteria to identify cows with this disease proposed by Sheldon et al. (2006) are widely used on dairy farms. This inflammation of the uterus results in fetid red-brown watery vaginal discharge, fever (>39.5 °C), and signs of systemic illness such as decreased milk yield, dullness, or other signs of endotoxemia. Bacteria isolated from the uterus of cows with metritis can be very diverse, including *Trueperella pyogenes*, *Escherichia coli*, *Fusobacterium necrophorum*, and *Prevotella* spp. (Sheldon and Dobson, 2004; Williams et al., 2005). Thus, broad-spectrum antibiotics are recommended as treatment options for metritis. Currently, an injectable oxytetracycline and ceftiofur are the most frequently used antimicrobials for metritis in dairy cows (Espadamala et al., 2018). Within the study cows, the puerperal metritis diagnosis was based on an enlarged and flaccid uterus with a foul-smelling uterine discharge regardless of fever. Our main findings were that primiparous cows have an increased risk for metritis. This is in agreement with the previous studies (Grohn et al., 1990; Kaneene and Miller, 1995; Dubuc et al., 2011). Primiparous cows have a greater risk for metritis than multiparous herdmates because of a greater need for calving assistance (Bell and Roberts, 2007; Ghavi Hossein-Zadeh and Ardalan, 2011). Abnormal calving usually requires human intervention, which increases the likelihood of bacterial contamination and uterine lesions, both leading to the development of metritis (Kaneene and Miller, 1995; Sheldon and Dobson, 2004). Currently, in the United States, only ceftiofur and injectable oxytetracycline are labelled as treatment options for metritis (Espadamala et al., 2018). In the set of cows used in our study, metritis cure with ceftiofur was

76.2%, which was consistent with others' results reporting that ceftiofur was an efficacious therapy for metritis in dairy cows (McLaughlin et al., 2012; Espadamala et al. 2018; Merenda et al. 2021).

In the current study, the overall prevalence of retained placenta and higher rate in multiparous cows was similar to reported previously (Rodríguez et al., 2017). Recent results presented by Caixeta et al. (2017), and supported by Neves et al. (2018), suggest that persistent subclinical hypocalcemia can be the main factor contributing to increases of a cow's risk of uterus disorders after calving. Rodríguez et al. (2017) reported a 78.2% prevalence of subclinical hypocalcemia with domination in multiparous cows, which were more likely to suffer retained placenta than primiparous cows. In addition, McArt and Neves (2020) reported that multiparous cows had a higher prevalence of delayed subclinical hypocalcemia with a higher risk of early lactation disease. Retained placenta traditionally belongs to risk factors for metritis (Grohn et al., 1990; Correa et al., 1993). However, there was no association between the retained placenta and metritis rate in our study. It is possible that a consecutive treatment of uterus atony and retained placenta contributed to the lower rate of metritis in the study. Previously, it was observed that treatment with carbetocin and $PGF_{2\alpha}$ elicited uterotonic effects in early postpartum cows resulting in a beneficial clinical effect on uterine involution and health during this period (Bajcsy et al., 2006; Drillich et al., 2006). Several studies demonstrated a negative effect of metritis on reproductive performance (i.e., increased calving to conception interval). Fourichon et al. (2000) reviewed some studies and found impaired reproduction in cows with metritis. The negative effects of metritis could affect fertility in many ways: first, through a delay in the return to cyclicity after parturition (Mateus et al., 2002; Sheldon et al., 2002); second, through a clear disruption of the uterine environment (BonDurant, 1999; Sheldon and Dobson, 2004); and third, through impairment of embryo development (Soto et al., 2003). In our study, ceftiofur treatment of metritis resulted in an unchanged inter-calving interval and no increased culling. Results from a previous study suggested that leaving metritis cases that occurred earlier in lactation within the first 8 DIM are less likely to recover and have more pronounced culling losses (Machado et al., 2020).

Metritis had negative effects on milk yield in our study. This is in agreement with previous reports that found lower milk production during early lactation in cows with metritis (Wittrock et al., 2011; Giuliodori et al., 2013). One reason for this effect could be that reduced feed intake in affected cows decreases the energy available for milk synthesis (Bell and Roberts, 2007; Wittrock et al., 2011). In fact, reduced intake has been detected even before parturition (Urton et al., 2005; Huzzey et al., 2007). However, the found negative association between metritis and milk production was not strong enough probably due to effective ceftiofur treatment. It is important to emphasize that the current recommendation of metritis therapy with ceftiofur can improve milk yield (Oliveira et al., 2020) and shorten the calving to conception of dairy cows (Piccardi et al., 2016; Oliveira et al., 2020). Results from a recent study showed that leaving metritis cases without treatment can lead to 732 kg less milk production in a year compared to metritis-treated cows (Machado et al., 2020).

CONCLUSIONS

In conclusion, we observed that treatment of the atonic uterus was not negatively associated with the reproductive and productive performance of dairy cows in spite of the high positive association with metritis. In addition, treatment of metritis resulted in similar reproductive performance compared to dairy cows without metritis. Moreover, ceftiofur treatment of metritis protected the cows from severe losses in milk production. In general, intensive monitoring and care of the reproduction health of dairy cows early after calving can decrease the risk of economic losses on dairy farms.

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