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Evaluation of intrauterine antibiotic treatment of clinical metritis and retained fetal membranes in dairy cows

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Abstract

Retained fetal membranes (RFM) and clinical metritis (CM) are frequently diagnosed disease conditions in dairy cows and considered of major economic impact due to negative effect on reproduction and milk production. The objective of this study was to evaluate the efficacy of i.u. tetracycline for the treatment of RFM and CM in dairy cows. Affected cows were randomly assigned to two groups; treatment group animals received i.u. 5 g chlortetracycline twice weekly for 2 wks, and no treatment group.

A total of 1416 cows and 804 heifers in 5 herds calved during the study period. CM was diagnosed in 18.6% (inter farm range; 15.2–23.5%) and 30% (19.4–42.3%) of cows and heifers, respectively. RFM was diagnosed in 13.1% (9.4–18.1%) and 9.2% (3.6–13.8%) of cows and heifers, respectively. Conception rates after first insemination were 38.3%, 42.5% and 18% in normal, treated and non-treated CM cows, respectively. Numbers of days open were 140.5, 136.2 and 165.5 in normal, treated and non-treated CM cows, respectively. Based on 305-d corrected milk yield, cows and heifers affected by RFM and CM produced 300–500 kg less milk compared with their normal herd mates. Cows treated for CM produced 654 kg more milk per 305-d corrected lactation compared to non-treated control cows. Treatment of RFM had no effect on reproductive performance or milk production. In conclusion, i.u. chlortetracycline treatment was proven to prevent the detrimental effect of CM on reproductive performance in heifers and cows and on milk production in cows only.

Keywords: Metritis; Retained fetal membranes; Treatment; Antibiotics; Dairy cows

1. Introduction

Retained fetal membranes (RFM) and metritis are frequently diagnosed disease conditions in dairy cows and considered of major economic impact due to negative effect on reproduction, milk production, increased culling rates and costs of treatments [1–3]. It is generally accepted that most cows with RFM will develop metritis to which most of the negative impact of RFM is attributed [4–7]. The diagnosis of RFM in dairy cows is simple and accurate although there are discrepancies between studies regarding time of onset postpartum [2,3]. Contrarily, diagnosis of primary metritis or endometritis in the early (<14 d) postpartum dairy cow is controversial and many researchers and practitioners refute this diagnosis [8,9]. It has been recommended to monitor the early postpartum cow for systemic signs of sepsis such as elevated rectal temperature, a condition referred to as toxic puerperal metritis (TPM) [10,11]. By this approach it was not recommended to examine or treat the early postpartum cow unless suffering from TPM and the appearance of fetid, watery vaginal discharge was considered as

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non-specific contamination with low predictive value for economical measures. Consequently it was recommended to routinely examine dairy cows only 3–4 wks after calving and to treat animals with abnormal vaginal discharge [9].

It was recently suggested to differentiate between puerperal metritis (PM) and clinical metritis (CM) both occurring within 21 d postpartum. While PM is synonymous with TPM, the diagnosis of CM was based on the presence of purulent vaginal discharge and enlarged uterus without systemic illness [12]. These authors also suggested defining cases with purulent vaginal discharge detected later then 21 d as clinical endometritis.

In the present study differentiation between PM and CM was not made and animals were diagnosed as having either RFM or CM as defined later. Metritis is a frequent diagnosis in Israeli dairy cows based on routine vaginal and rectal examination performed 5–14 d after calving [13,14]. Since similar routine examination of dairy cows in the first 2 wks after calving is not commonly practiced in Europe or North America, most recent studies enrolled either cases of PM or clinical endometritis diagnosed within and later than 3 wks postpartum, respectively.

Treatment protocols for CM or RFM are highly controversial and although intrauterine antimicrobials, especially tetracyclines, are used extensively their efficacy was questioned [15,10,16,6]. Outcome variables for treatment efficacy trials should be measures of economic significance, such as milk production and reproductive performance, rather than clinical or bacteriological cure.

The objectives of this study were to analyze the impact of RFM and early CM on milk production and reproductive performance in dairy cows. Concurrently, the efficacy of the commonly used i.u. tetracycline treatment for RFM and CM was evaluated in a randomized, negatively controlled, multi-herd field trial analyzed as a prospective cohort study with milk production and reproductive parameters as outcome variables. Evaluation of treatment efficacy for RFM and CM will be based on elimination or reduction of the expected negative effect of these conditions on milk production and reproductive performance.

2. Material and methods

2.1. Animals and herds

The study was conducted on cows calved between April 2000 and December 2001 in five commercial Israeli dairy herds consisting of 250–350 Israeli Holstein dairy cows. Cows were housed in loose housing systems in large, completely covered open sheds and fed total mixed ration (TMR). In all herds, cows were milked three times daily in computer controlled milking parlors and the mean annual milk production was 10,000–12,000 kg per cow. All cows were identified by ear tags and freeze marking. The herds were within the practice area of the Ambulatory Clinic of The Koret School of Veterinary Medicine, which provided a complete herd-health service and all herds were visited at least twice weekly during the trial period. Clinical, reproduction, production and management data were computer recorded by the herd manager and the attending veterinarians. Once a month each cow was sampled and analyzed for milk, fat, protein, and lactose production and somatic cell count by the Central Laboratory for Milk Recording. Reproductive management was solely based on AI performed by highly trained technicians employed by the Artificial Insemination Service of the Israel Cattle Breeders Association (ICBA). In all herds, cows were bred on observed estrus or computerized pedometry system and no timed breeding protocols were used. Pregnancy diagnosis was performed by rectal palpation of the uterus and its contents 40–50 d post insemination.

2.2. Clinical examination

All heifers and cows were examined between 5 and 14 d after calving by trained veterinarians who also diagnosed, treated and recorded all the periparturient disease conditions. At examination all animals were body scored and comprehensively examined by intravaginal and transrectal palpation after thoroughly cleaning and disinfection of the perineal area. Cases of retained fetal membranes (RFM) were defined as the presence of placental tissues 24 h or more after calving as observed by trained farm employee or the attending veterinarian. Animals with observed or suspected RFM were submitted for veterinary examination on the next routine biweekly visit (1–4 d postpartum). In animals without a history or diagnosis if RFM, the diagnosis of clinical metritis (CM) was based on the combined characteristics of vaginal discharge, obtained by manual examination of the vagina, and of cervical and uterine examination by palpation per rectum as previously described [17]. Affected cows had a flaccid, nonretractable uterus that was located in the abdomen, a cervical diameter >75 mm, and a watery or purulent, fetid vaginal discharge.

All cows with lower-than-expected milk production and poor appetite were examined for ketosis by placing a drop of urine obtained with a disposable plastic catheter on a reagent strip (Ketostix, Ames, England) and comparing the color of the reaction after 15 s with a standardized color chart. Cows with urine AcAc concentration $\geq$15 mg/dl were recorded as ketotic.

Body condition scoring (BCS) was further recorded before dry-off and approximately 60 d after calving. Heifers and cows pregnant longer than 276 and 278 d, respectively, were examined and calving was induced with prostaglandin F2α analogue (Estrumate 500 μg i.m.) if oversized fetus was estimated.

All animals not observed in estrus by the end of the voluntary waiting period (90–120 d for primiparous and 80–100 d for multiparous cows) were recorded and submitted for examination. Ovaries were palpated per rectum and findings were recorded, animals without a palpable CL were resubmitted for examination a week later if not observed in estrus. Animals without a palpable CL in the two consecutive examinations were recorded as anestrous cows.

2.3. Treatment

All heifers and cows calving during the study period participated in the clinical trial. At the conclusion of the clinical examination, animals with either CM or RFM were randomly assigned to receive 5 g chlortetracycline (Tetracycline uterine pessaries, Vitamed, Israel) by i.u. installation, twice weekly for 2 wks or no treatment. Treatment was randomized by using the brand numbers of the cows, all odd-numbered cows were allocated to one treatment group, and even-numbered cows to the other group. Animals in the no treatment, the negative control group, were subjected to the same examination routine as the treatment group cows.

At any stage, no attempt was made to manually remove the retained fetal membranes. On each examination slight external traction was applied in an attempt to remove fetal membranes that were completely separated from the uterus.

2.4. Statistical analysis

Computerized data were retrieved from the herds and ICBA central computer and analyzed using Excel (version 2000, Microsoft, Redmond, WA) and SPSS 10.0.1 (SPSS Inc., Chicago, IL, USA). Lactational Incidence Risk (LIR) for all recorded diseases and reproductive performance parameters were evaluated for cows in the trial groups; treated and non-treated cows with RFM, treated and non-treated cows with CM, and normal cows. Reproductive performance parameters included days to first AI, first AI conception rate, days open, proportion of cows not pregnant >150 d after calving, proportion of cows not observed in estrus before first AI, and the proportion of anestrous cows before first AI.

The effects of RFM, CM and treatment thereof on dichotomous outcome variables were evaluated using binary logistic regression modeling.

Using time to pregnancy and time to first insemination as time variables, Kaplan–Meier survival analysis was performed to compare the effects of RFM, CM and treatment thereof. Cows contributed a maximum of 150 d to the analysis and observations were censored when a cow died, culled or was excluded from breeding. Based on monthly test days milk yields, the individual 305-d corrected milk production was calculated [18]. Multivariable linear regression modeling was used to analyze 305-d adjusted milk production. Separate analysis was conducted for first (primiparous heifers), and second and above lactation cows. Uterine disease and treatment status was included in the models as an independent variable and various parameters and disease conditions were tested in the models as possible confounders. These included; length of the dry period, BCS, calving season (Summer: April–August; Winter: September–March), twin calving, ketosis, milk fever, and displaced abomasums, stillborn calves and induction of calving. Crude bivariate associations of outcome and potential confounding variables with treatment were initially assesses by use of Pearson χ^2 asymptotic two-sided tests of significance. To build the models, the treatment variable was forced into the model and subsequent covariates were analyzed by use of forward stepwise procedure with entry criteria set at $P < 0.05$ and exit criteria set at $P > 0.10$. For all analyzes, values of $P < 0.05$ were considered significant.

3. Results

3.1. Descriptive statistics

During the study period a total of 1416 multiparous cows and 804 primiparous heifers calved and submitted for routine postpartum examination. CM was diagnosed in 18.6% (inter farm range; 15.2–23.5%) and 30% (19.4–42.3%) of cows and heifers, respectively. RFM was diagnosed in 13.1% (9.4–18.1%) and 9.2% (3.6–13.8%) of cows and heifers, respectively (Table 1). In 967 cows (68.3%) and 489 heifers (60.8%), no uterine abnormality was diagnosed and were classified as

Table 1
Number of animals affected by retained fetal membranes (RFM) and postparturient clinical metritis and the lactational incidence rates (%) of these conditions in the study dairy herds (farm)

Farm	RFM				Metritis				Normal		Total	
	Heifers		Cows		Heifers		Cows		Heifers	Cows	Heifers	Cows
	n	%	*n*	%	*n*	%	*n*	%	*n*	*n*	*n*	*n*
A	14	8.2	33	11.1	33	19.4	45	15.2	123	219	170	297
B	22	12.6	51	18.1	48	27.4	43	15.3	105	187	175	281
C	6	3.6	27	9.4	46	27.5	60	20.9	115	200	167	287
D	14	8.6	44	15.1	59	36.4	55	18.9	89	192	162	291
E	18	13.8	30	11.5	55	42.3	61	23.5	57	169	130	260
Total	74	9.2	185	13.1	241	30.0	264	18.6	489	967	804	1416

Table 2
Descriptive data of mean reproductive performance variables in normal cows and heifers and these affected by retained fetal membranes (RFM) and postparturient clinical metritis randomly divided into treatment and non-treatment control groups

Parameter	RFM				Metritis				Normal	
	Heifers		Cows		Heifers		Cows		Heifers	Cows
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control		
1st AI conception rate (%)	41.9	38.7	33.3	34.3	47.4	34.0	42.5	18.0	46.8	38.3
Not observed in estrus (%)	23.1	28.6	22.3	22.2	32.8	15.7	22.4	30.0	18.3	22.8
Anestrus (%)	2.6	5.7	6.4	4.4	12.6	6.6	9	6.2	4.6	5.9
Not pregnant >150 d	26.1	37.5	24.5	36.0	34.5	42.0	29.4	45.1	30.8	32.1
Days open	149.2	149.6	135.4	143.5	147.9	146.4	136.2	165.5	139.6	140.5
Days to 1st AI	108.8	106.9	99.7	104.5	114.5	109.7	104.6	105.9	110.6	103.8

normal. Intrauterine tetracycline treatment was administered to 95 cows and 39 heifers with RFM and 134 cows and 120 heifers with CM. 90 cows and 35 heifers with RFM and 130 cows and 121 heifers with CM, served as non-treated controls.

3.2. Impact of uterine diseases and treatment on reproductive performance

Mean numbers of days to first service (AI) and to pregnancy (days open) of normal, treated and non-treated RFM and CM cows and heifers are presented in Table 2. In normal, treated and non-treated CM cows, mean numbers of days to first AI were 103.8, 104.6, and 105.9 d, respectively. Mean numbers of days open were 140.5, 136.2 and 165.5 in normal, treated and non-treated CM cows, respectively. Survival analysis compared time to first insemination and time to pregnancy for normal, treated and non-treated CM and RFM cows and heifers. Of these entire outcome variables only treated versus non-treated CM cows and normal versus non-treated CM cows differed significantly using the log-rank test ($P = 0.0088$ and 0.0354, respectively) (Fig. 1).

Conception rates after first insemination of normal, treated and non-treated RFM and CM cows and heifers are presented in Table 2. Conception rates after first insemination were 38.3%, 42.5% and 18% in

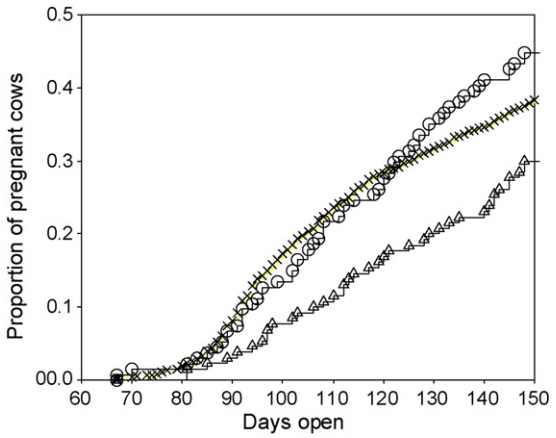

Fig. 1. Kaplan–Meier survival analysis: relationship of proportion of pregnant cows and days open for cows treated for CM (○), non-treated controls (▽) and normal cows (×). Treated vs. non-treated CM cows and normal vs. non-treated CM cows differed significantly using the log-rank test ($P = 0.0088$ and 0.0354, respectively).

Table 3
Summary of binary logistic regression model of the impact of experimental animal group status (normal, treated, non-treated control) on conception on first insemination in animals with retained fetal membrane (RFM), postparturient clinical metritis (CM) and normal animals

Uterine disease	Parameter	B	S.E.	Wald	d.f.	Sig.	OR	95% CI	
RFM	Farm	0	0	7.829	1	0.005	1.000	1.000	1.000
	Calving season[a]	−0.329	0.117	7.846	1	0.005	0.720	0.572	0.906
	Non-cyclic[b]	−0.689	0.28	6.04	1	0.014	0.502	0.290	0.870
	Animal group								
	Normal[c]	0.595	0.211	7.953	1	0.005	1.813	1.199	2.742
	Treatment[d]	0.021	0.28	0.006	1	0.939	1.022	0.590	1.769
	Control[e]	(Reference)					1.000		
	Parity								
	1	0.481	0.139	11.951	1	0.001	1.618	1.232	2.125
	2	0.152	0.144	1.126	1	0.289	1.165	0.879	1.544
	3	(Reference)					1.000		
	Constant	−1.664	0.334	24.826	1	0.000	0.189		
CM	Farm	0.000	0.000	6.318	1	0.012	1.000	1.000	1.000
	Calving season	−0.229	0.108	4.476	1	0.034	0.795	0.643	0.983
	Parity								
	1	0.553	0.129	18.339	1	0.000	1.739	1.350	2.241
	2	0.220	0.138	2.545	1	0.111	1.246	0.951	1.633
	3	(Reference)					1.000		
	Animal group								
	Normal	1.006	0.168	35.805	1	0.000	2.736	1.967	3.804
	Treatment	0.794	0.202	15.515	1	0.000	2.212	1.490	3.284
	Control	(Reference)					1.000		
	Constant	−2.078	0.304	46.652	1	0.000			

[a] Calving season: April–August = summer calving.
[b] Non-cyclic: animals without active corpus luteum on at least 2 consecutive weekly examinations.
[c] Normal: animals free of RFM or metritis.
[d] Treatment: treated RFM or metritis group.
[e] Control: non-treated RFM or metritis control group.

normal, treated and non-treated CM cows, respectively. The logistic regression model indicated that treatment for CM of both heifers and cows significantly affected the risk of conceiving after first service. Conception rates after first service of normal cows and heifers were not significantly different compared to treated animals affected by CM. In the final model, including farm and not observed in estrus as covariates, the OR of a treated heifer with CM to conceive after first service compared to non-treated control was 2.088 (95% CI 1.132–3.85, $P = 0.018$). The OR of a treated cow with CM to conceive after first service compared to non-treated control was 2.309 (95% CI 1.111–4.797, $P = 0.025$), including anestrus and BCS at calving as covariates. Summary of the combined final logistic regression model of the association between animal group status and conception after first service in heifers and cows is presented in Table 3.

The negative effect of RFM on conception rates after first service was considerably smaller than that observed for CM. Treated and non-treated RFM cows had first service conception rates of 33.3% and 34.3%, respectively, compared to 38.3% in normal cows. In primiparous heifers, treated and non-treated RFM heifers had first service conception rates of 41.9% and 38.7%, respectively, compared to 46.8% in normal heifers. However these smaller differences were statistically significant in the final logistic model and the OR of a normal animal to conceive after first service compared to non-treated control animal with RFM was 1.813 (95% CI 1.199–2.742, $P = 0.005$). Contrary to CM in cows, no statistically significant differences were found between treated and non-treated cows and heifers with RFM (Table 3).

3.3. Impact of uterine disease and treatment on milk production (Table 4)

Complete data for milk production analysis was available from 601 primiparous heifers and 1230 multiparous cows. Both RFM and CM significantly

Table 4
Summary of multivariable linear regression model of the impact of experimental animal group status (normal, treated, non-treated control) on 305-d corrected milk production in animals with retained fetal membrane (RFM), postparturient clinical metritis (CM) and normal animals

Uterine disease	Animal group	Parameter	B	S.E.	*t*	Sig.
RFM	Heifers	Constant	8893.11	378.611	23.49	0.0000
		Normal[a]	319.281	256.55	1.24	0.2140
		Treatment[b]	260.032	337.726	0.77	0.4418
		Control (reference)[c]				
		Farm	0.00154	0.000544	2.84	0.0048
		Calving season	−293.754	121.704	−2.41	0.0162
	Heifers	Constant	10089.129	683.479	14.761	0.000
		Normal	411.915	191.957	2.146	0.033
		Treatment + control	(Reference)			
		Farm	0.0019	0.001	3.347	0.001
		Calving season	−360.158	129.752	−2.776	0.006
		BCS60	−479.672	198.541	−2.416	0.016
	Cows	Constant	11668.785	779.564	14.968	0.000
		Normal	537.474	231.284	2.324	0.020
		Treatment	−206.944	309.844	−0.668	0.504
		Control (reference)				
		Farm	0.0016	0.001	3.13	0.002
		Parity	285.317	49.912	5.716	0.000
		Calving season[d]	−558.421	127.483	−4.38	0.000
		BCS60[e]	−894.2840	167.658	−5.334	0.000
		Days dry	15.185	7.361	2.063	0.039
CM	Heifers	Constant	8870.959	287.551	30.85	0.000
		Normal	337.73	145.26	2.325	0.020
		Treatment	17.739	179.793	0.099	0.921
		Control (reference)				
		Farm	0.0015	0.0000	3.381	0.001
		Calving season	−287.399	105.077	−2.735	0.006
	Cows	Constant	12509.6	556.983	22.46	0.000
		Normal	498.212	198.141	2.514	0.012
		Treatment	656.225	253.625	2.587	0.010
		Control (reference)				
		Farm	0.0015	0.0000	3.17	0.002
		Parity	309.785	46.792	6.62	0.000
		Calving season	−532.3410	122.7780	−4.336	0.000
		BCS60	−848.719	158.01	−5.371	0.000

[a] Normal: animals free of RFM or CM.
[b] Treatment: treated RFM or CM group.
[c] Control: non-treated RFM or CM control group.
[d] Calving season: April–August = summer calving.
[e] BCS60: body condition scoring 60 d postpartum.

reduced milk production in heifers and cows; non-treated RFM and CM animals were compared with normal animals (Table 4). The difference in milk production was not statistically significant when normal heifers were compared to non-treated RFM animals probably due to the small number of animals in this group. Since no statistically significant difference was found between treated and non-treated RFM heifers, these two groups were combined and compared with normal heifers (Table 4). Heifers and cows affected by RFM produced 412 and 537 kg less 305-d corrected milk, respectively, compared to normal animals (Table 4). Heifers and cows affected by CM produced 338 and 498 kg less 305-d corrected milk, respectively, compared to normal animals (Table 4).

Milk production of treated animals affected by RFM or treated heifers with CM was not statistically significantly different from their non-treated controls. However, treated CM cows produced 656 kg more than the non-treated CM controls, indicating the efficacy of

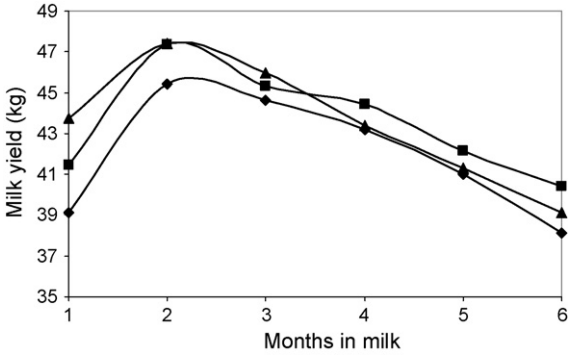

Fig. 2. Lactation curves based on monthly test days milk yields of normal cows (▲), cows treated for metritis by i.u. chlortetracycline (■), and non-treated control cows with metritis (◆).

the treatment protocol for the prevention of milk loss due to CM in cows. Lactation curves of these groups show the differences in the mean monthly test days milk yield. Differences were most pronounced in early lactation (Fig. 2).

4. Discussion

Dairy herd-health in Israel is based on routine veterinary examination of all cows 5–14 d after calving and early intrauterine treatment of cows with RFM (1–4 d) and CM (5–14 d) [13,19]. Recent studies advocated to replace early postpartum clinical examination with monitoring of milk production and rectal temperature as indicators of systemic disease and the development of PM or TPM due to RFM or metritis. These studies also concluded that local intrauterine antimicrobial treatment should be replaced by systemic treatment only for cows showing signs of systemic disease mainly indicated by elevated rectal temperatures [16,6]. However, as previously published, solely monitoring rectal temperature of postpartum dairy cows has lower predictive value for uterine infection than including vaginal examination for abnormal uterine discharge [20].

This study addressed two important questions; the predictive value for milk production and reproductive performance of early postpartum diagnosis of CM based on vaginal and rectal examination of the genital tract, and efficacy of early i.u. administration of tetracycline for the treatment of RFM and CM.

The LIR of CM and RFM described in the present study were within the range previously reported for dairy herds, though diagnostic techniques and case definition vary between studies [13,19,21–23,3]. Considerable variations were observed between farms, which was a significant covariate in all the models.

In the present study, CM in multiparous cows was associated with 20% lower conception rate after first service and 25 more days to conception. This impact of CM on reproductive performance was similar to meta-analysis results of several research studies [2]. The impact of RFM on reproduction, although statistically significant, was considerably smaller and similar to that described in previous studies [2].

Based on 305-d corrected milk yield, cows and heifers affected by RFM and CM produced 300–500 kg less milk compared with their normal herd mates. Most studies using models with a 305-d milk yield failed to show association of RFM or metritis with decreased milk yield explained by failure to capture the short term fluctuations in milk production induced by the disease [24,1,18]. In the present study, non-treated RFM and metritis cases were compared to normal cows while in most previous studies all affected animals were treated. Although treatment of RFM was indifferent, CM treatment eliminated the 305-d milk yield difference between non-treated CM and normal cows. This difference would have been missed if normal animals were to be compared to treated animals.

The overall effect of intrauterine chlortetracycline treatment was most pronounced for multiparous cows affected by CM. Milk production and reproduction parameters of CM treated cows were similar to these of their normal herd mates.

Based on the same outcome variables, intrauterine tetracycline treatment of RFM was not effective. Considering the fact that cows with RFM develop CM, failure of the same treatment that was effective for primary CM might indicate that this therapeutic protocol is detrimental in RFM cows. The i.u. chlortetracycline treatment before placental separation and expulsion might have retarded cotyledon-carancular separation exacerbating endometrial damage [11]. However, in previous studies, intrauterine oxytetracycline treatment did not extend retention time [15] and the incidence of endometritis after RFM was reduced from 76% to 16% [7].

Although RFM and CM significantly affected milk production and reproduction in primiparous heifers, treatment was generally ineffective in this age group. These disease conditions although seems similar in multiparous and primiparous animals might have different etiologies and pathogenesis in these age groups [18].

The selected dosage regimen in this study was based on previously reported pharmocokinetic and uterine microbial sensitivity studies. However, since all treatments were administered by veterinarians, the study

protocol had to confer with routine farm visits. Chlortetracycline is a time dependent, bacteriostatic antibiotic with no post antibiotic effects. Although a high dose was used in this study, it is unknown if bacteriostatic levels were obtained in the uterine wall and lumen following i.u. administration of 5 g chlortetracycline twice weekly. It is also noteworthy that bacteria cultured from RFM and CM cases in Israel and the UK were generally resistant to tetracyclines [25–27]. The efficacy of intrauterine tetracycline might be related to other uncultured or unknown organisms sensitive to this antimicrobial. However, the efficacy might also be related to non-antimicrobial effects of tetracyclines, which also display anti-inflammatory effects. Tetracyclines are potent inhibitors matrix metalloproteinases (MMP) and inducible Nitric Oxide Synthase (iNOS), which are known to play a role in the mediation and control of mucosal inflammation and immune response [28,29]. Both these mechanisms and the antimicrobial effect of tetracycline might also be related to the observed therapeutic failure of RFM, as placental separation is probably dependent on adequate function of immune cells, proteolytic enzymes and microbial activity [3,30,11].

Daily intrauterine infusion of 5 g oxytetracycline in cows with RFM was reported to result in illegal milk residues [31]. Although all farm bulk tank milk was sampled for antimicrobial residues before transportation, no illegal antibiotic residues were found during the study period. This difference might be explained by the different dosage regimen (once daily versus twice weekly), drug preparation (infusion versus pessaries), detection systems or bulk tank milk dilution.

In conclusion our diagnostic criteria for early CM seem to have high predictive value for milk loss and lowered reproduction both in primiparous heifers and multiparous cows. Based on milk production and reproductive performance as outcome parameters, twice weekly i.u. instillation of 5 g chlortetracycline in the form of pessaries was not effective for the treatment of RFM. This same treatment was highly effective for the treatment of CM in cows. However, residue studies have to be done to ensure that this therapeutic regimen does not lead to illegal levels of chlortetracycline in the milk. To minimize the negative effect of RFM on milk production and reproductive performance, alternative treatment protocols will have to be evaluated.

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