Effect of intrauterine administration of ceftiofur on fertility and risk of culling in postparturient cows with retained fetal membranes, twins, or both

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Objective—To determine the effect of intrauterine administration of ceftiofur sodium on fertility and the risk of culling in postparturient cows with retained fetal membranes (RFM), twins, or both.

Design—Single-blind randomized clinical trial and prospective cohort study.

Animals—2,442 cows that calved from January 1, 2000, to May 31, 2001.

Procedure—Cows with RFM, twins, or both were randomly allocated to control or treatment (ceftiofur) groups. Ceftiofur-group cows received 1 g of ceftiofur sodium sterile powder reconstituted with 20 mL of sterile water as a single intrauterine infusion once between 14 and 20 days after parturition. Control-group cows received no treatment. Cows that calved but did not have RFM or twins were considered the referent group. Reproductive, culling, and health data were recorded.

Results—There was no significant difference in the overall proportion of ceftiofur-group cows confirmed pregnant, compared with cows in the control group. Ceftiofur-group cows were significantly less likely to be culled and were culled at a later time in lactation than control-group cows. In the cohort study, the risk of pregnancy and the risk of being culled in ceftiofur-group cows were not significantly different from cows in the referent group.

Conclusions and Clinical Relevance—Intrauterine treatment of cows with RFM, twins, or both with ceftiofur sodium increased longevity of cows in the herd as measured by the risk of culling and the time to culling. Intrauterine administration of ceftiofur in cattle is considered extralabel drug use, and the attending veterinarian must follow the AMDUCA guidelines for extralabel drug use. (*J Am Vet Med Assoc* 2005: 226:2044–2052)

RUMINANTS

Retained fetal membranes (RFM) and twinning in dairy cows have consistently been found to increase the risk for several postpartum disorders,[1] affect subsequent reproductive efficiency,[2,3] increase calf death loss,[1] and result in higher risk for culling.[4] In 2001, Johanson et al[5] reported that a higher twinning rate exists in daughters of sires born after 1990 (5.58%), compared with daughters of sires born before 1990 (4.55%).[5] As production levels improve, twinning rate increases[6,7]; therefore, as genetic and nutritional progress continues, an increase rather than a decrease in twinning can be expected. Although twinning (perhaps through changes in genetic selection) and RFM would ideally be prevented, in reality, these conditions will continue to cause problems in dairy cows. Various preventive methods have been investigated, such as the addition of selenium to rations,[8] incorporation of rations with a negative dietary cation-anion difference in the prepartum period,[9] and manual reduction of twin pregnancies. After RFM are detected or twin delivery has occurred, various treatments including administration of prostaglandins,[3] oxytetracycline,[10] estrogenic compounds,[10] or manual removal of RFM[11] have been used without improvement in subsequent fertility. In large-scale modern dairies, treatment protocols developed in consultation with herd veterinarians (that animal health managers and team members apply based on the problem identified) are established. These protocols include standardized recommendations for various health conditions, including RFM and complications associated with twinning.

To the authors' knowledge, studies concerning the effect of intrauterine administration of ceftiofur sodium on subsequent fertility in dairy cattle have not been reported; however, in 1995, Bermúdez et al[12] reported that intrauterine infusion of ceftiofur sodium after a low-volume uterine flush in barren mares improved conception 40 days after insemination and foaling rates and decreased the number of services required. The purpose of the study reported here was to determine whether intrauterine administration of ceftiofur sodium to cows with **RFM, twins, or both (RFM/T)** would increase the proportion of cows determined to be pregnant at the first **timed artificial insemination (TAI)**, increase overall conception rates at all inseminations, decrease the calving to conception interval (time to pregnancy), decrease the overall risk of culling and the risk of culling for reproductive reasons, increase longevity in the herd, and return these 4 parameters to near baseline, compared with herdmates without RFM/T.

Materials and Methods

Farm description and data collection—A herd of 2,000 Holstein cows in central Texas producing > 11,000 kg (24,200 lb) of milk annually was used in the study. The herd

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was milked 3 times daily. The herd owner subscribed to the state dairy herd improvement services[a] and used an on-farm, computer-based record-keeping system[b] for production and health data. All health, production, and reproduction data pertaining to this study were collected as part of the standard operating procedures of the dairy farm.

The herd was managed and fed similar to many of the large herds in the county and in the immediate region. Briefly, the milking herd was housed primarily in free stall barns, with late lactation cows in drylots. Immediately after parturition, specimens were obtained from the udders of cows for bacteriologic culture for standard organisms that cause mastitis (*Staphylococcus* spp, *Streptococcus* spp, coliforms, and *Arcanobacterium [Actinomyces] pyogenes*) and *Mycoplasma* spp. Cows in which *Mycoplasma* spp were detected were culled. Selective treatment for mastitis was used depending on the other organisms that were identified. The herd was fed a total mixed ration with corn silage and alfalfa hay as the primary forages with some wheatlage and sorghum silage. Corn (ground and steamrolled), soybean meal, whole cottonseed, and a vitamin-mineral package were included in the concentrate portion of the ration throughout the study. Fans and soakers were used in the holding pen and feed lanes for heat abatement during periods of heat stress. The herd was vaccinated against leptospirosis, brucellosis, infectious bovine rhinotracheitis, bovine viral diarrhea, parainfluenza, clostridial diseases, and coliform mastitis.

Cows not in lactation and heifers were housed in separate pens prior to parturition; these cows received anionic salts in their ration for approximately 2 weeks prior to parturition. Personnel attending calving recorded the time of birth, sex of the calf (or calves), ease of calving (by use of a National Association of Animal Breeders 1-to-5 scale[c]), and number of calves born. Cows with a calving ease score ≥ 3 received 4 mg of **estradiol cypionate**[d] **(ECP)** immediately after calving. Cows that had not expelled the fetal membranes by 24 hours after parturition were classified as having RFM and were given 4 mg of ECP. Cows were moved into early postpartum management groups; primiparous and multiparous cows were maintained in separate groups. For all cows, rectal temperatures were obtained daily for the first 10 days after parturition. Any cow with pyrexia (rectal temperature > 39.5°C [103.1°F]) received ceftiofur hydrochloride sterile suspension[e] (2 mg/kg [0.91 mg/lb], IM) daily for 5 consecutive days. In addition to recording calving events (eg, calving difficulty or RFM/T) and daily rectal temperatures, cows not in lactation and periparturient and lactating cows were observed daily and health problems such as metritis, bovine parturient paresis, mastitis, ketosis, displaced abomasum, lameness, and diarrhea were recorded. Reasons for cows leaving the herd were recorded according to standard Dairy Herd Improvement Association codes.[b] The herd owner used HeatSynch or OvSynch preceded by PreSynch programs to breed all cows by TAI from day 70 to 76 of lactation, as described previously.[13] All prescribed and scheduled injections and treatments for these programs and other indications were likewise recorded, as were TAI and bull breeding events, confirmed pregnancies, and any observed or presumed abortions.

The sampling frame for this study included any cow calving from January 1, 2000, through May 31, 2001. Lactation was the period of interest for a cow; for cows that calved twice during the study, only the lactation recorded first was used in the analysis. Cows were included in the analysis if they completed a full lactation and entered the next lactation with a subsequent calving date recorded or they left the herd (eg, culled, sold for dairy purposes, or died) and the date and reason for departure were recorded.

Single-blind randomized clinical trial—The clinical trial was performed to compare the efficacy of intrauterine administration of ceftiofur sodium in cows with RFM/T (ceftiofur group; n = 101) and cows with RFM/T in which ceftiofur sodium was not administered (control group; 106).

Each Monday during the study, the herd veterinarian performed a rectal examination on cows that were scheduled (by day 21 after parturition) to be moved from the early postpartum group. Cows that had RFM/T were randomly allocated to control or ceftiofur groups on an alternating basis. The randomization scheme was as follows: eligible cows were blocked by week and listed by age to distribute cows of similar age between groups, and the oldest cow in the list was allocated to either the control or ceftiofur group by flipping a coin, then the next oldest cow down the list received the alternate treatment; this was repeated in sequence until the block of cows for the entire week was allocated. The random allocation list was prepared offsite by 1 of the authors (ERJ) using the list of eligible cows. The herd manager and staff were unaware of treatment-group allocations. Cows in the ceftiofur group received 1 g of ceftiofur sodium sterile powder[f] reconstituted in 20 mL of sterile water as a single intrauterine infusion once between 14 and 20 days after parturition, which was administered by the attending veterinarian. If scheduling conflicts precluded administration of ceftiofur on the prescribed date, the block of cows for the entire week were excluded from the trial. Any cows leaving the herd (ie, sold for dairy purposes, culled, or died) prior to 21 days in lactation were also excluded from the trial. Reproductive, culling, death, and health data were recorded as previously described.

Prospective cohort study design—The prospective cohort study was performed to compare the reproductive performance and risk of culling of cows with RFM/T that had received an intrauterine infusion of ceftiofur sodium (ceftiofur group; n = 101) with those cows calving in the herd without RFM/T (referent group; 2,235)

Cows that calved from January 1, 2000, through May 31, 2001, but did not have RFM/T were considered as an additional comparison group (referent group). Only lactations represented by the first recorded calving event occurring during the study were used. Cows leaving the herd before 21 days in lactation were excluded from the analysis. Definitions for RFM/T (or lack thereof) and treatment-group allocation for the clinical trial were used to define the comparison cohort (ie, ceftiofur-group cows). Statistical analyses performed on data from these cows were designed to evaluate how close the treatment was capable of returning each of the outcome variables to performance levels that were considered normal for this herd, adjusted for potential confounders such as age and other comorbidities.

Statistical analyses—All statistical analyses were performed by use of computer software.[g] For this herd, previous experience indicated that cows with RFM/T would be expected to have slightly < 50% overall conception per lactation, compared with slightly > 70% for the rest of the herd. For the single-blind randomized trial, sample size requirements were estimated as follows: we wanted an 80% chance of detecting a true difference between groups if one existed, with a 5% probability of type I error to demonstrate an absolute difference of 20% between cows in the ceftiofur and control groups, assuming that intrauterine treatment with ceftiofur sodium would return fertility to near 70% conception per lactation. These criteria indicated that 94 cows/treatment group were required. Entry to the study was stopped when a minimum of 100 cows had been allocated to each group.

Descriptive statistics were cross-tabulated by treatment for each of the outcome variables (the number of cows confirmed pregnant at first TAI, number of cows confirmed pregnant from any insemination, number of cows calving at a subsequent lac-

tation, number of cows that were culled, number of cows that were culled for reproductive reasons only, number of cows that died, time to pregnancy, and time from calving to culling) and for other variables considered to have the potential to confound or interact with treatment when assessing the effects on outcome variables. This latter group of variables included the number of days a cow was not in lactation during the previous lactation, age (in months and by lactation), number of cows delivering a stillborn calf (or calves), number of cows delivering twins, number of cows with RFM, and diseases recorded prior to 100 days in lactation (pyrexia, metritis, ketosis, first and second episodes of mastitis, displaced abomasums, bovine parturient paresis, diarrhea, and lameness). Those cows culled early, bred early, or not receiving the full complement of treatments incorporated in the synchronization programs were excluded from the analysis of cows confirmed pregnant at first TAI. Crude bivariate associations of outcome and potential confounding variables with the treatment were initially assessed by use of Pearson χ^2 asymptotic 2-sided tests of significance. Covariates measured on a continuous scale were assessed for significance by use of a 2-sided *t* test, largely to assess equivalent distribution of treatment groups via the randomization process. Time to event outcomes were assessed as to survival distribution (overall and by treatment) by use of the nonparametric Kaplan-Meier method, and survival curves were plotted and assessed by treatment group by use of the log-rank test.

The covariate-adjusted effects of treatment on each of the categorical outcome variables were assessed in a multi-

Table 1—Frequencies (percentage) for outcome variables in cows with retained fetal membranes (RFM), twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group) from 14 to 20 days after parturition, compared with cows with RFM, twins, or both that received no treatment (control group) or cows that calved but did not have RFM or twins (referent group).

		RFM, twins, or both (Stratified by treatment)					
Outcome variable	**Response**	**Control (n = 106)**	**Ceftiofur (101)**	***P* value***	**Referent (2,235)**	***P* value†**	**Total (2,442)**
Confirmed pregnant at first TAI‡	No	62 (82.7)	54 (75.0)	0.255	1,223 (70.3)	0.390	1,339 (71.0)
	Yes	13 (17.3)	18 (25.0)		517 (29.7)		548 (29.0)
Confirmed pregnant from any insemination	No	50 (47.2)	37 (36.6)	0.125	588 (26.3)	0.022	675 (27.6)
	Yes	56 (52.8)	64 (63.4)		1,647 (73.7)		1,767 (72.4)
Subsequent calving in this herd	No	70 (66.0)	50 (49.5)	0.016	892 (39.9)	0.055	1,012 (41.4)
	Yes	36 (34.0)	51 (50.5)		1,343 (60.1)		1,430 (58.6)
Culled	No	41 (38.7)	56 (55.4)	0.016	1,403 (62.8)	0.137	1,500 (61.4)
	Yes	65 (61.3)	45 (44.6)		832 (37.2)		942 (38.6)
Culled for reproductive reasons	No	72 (67.9)	86 (85.1)	0.004	2,066 (92.4)	0.220	2,239 (91.7)
	Yes	34 (32.1)	15 (14.9)		169 (7.6)		203 (8.3)
Died	No	100 (94.3)	96 (95.0)	0.820	2,173 (97.2)	0.200	2,369 (97.0)
	Yes	6 (5.7)	5 (5.0)		62 (2.8)		73 (3.0)

**P* values were derived from an asymptotic Pearson χ^2 2-sided test of association (unadjusted) comparing cows in the ceftiofur group with cows in the control group. †*P* values were derived from an asymptotic Pearson χ^2 2-sided test of association (unadjusted) comparing cows in the ceftiofur group with cows in the referent group. ‡Cows considered ineligible for the first timed artificial insemination (TAI) were excluded from this analysis. This included cows culled or bred early and cows not receiving the full complement of treatments incorporated in the 2 synchronization programs.

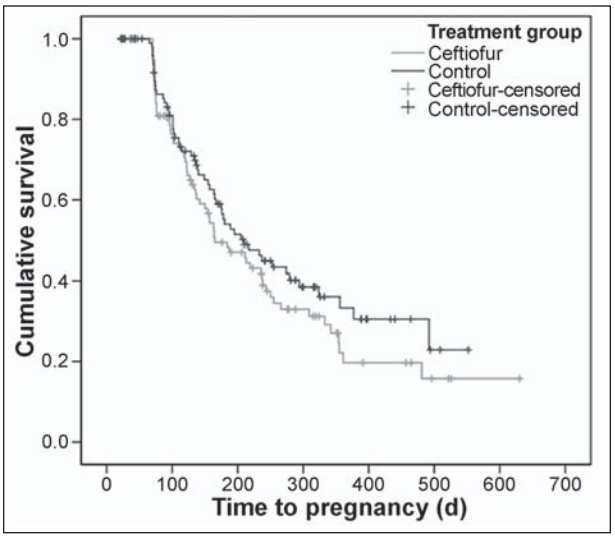

Figure 1—Kaplan-Meier survival curves for analysis of time to pregnancy in cows with retained fetal membranes (RFM), twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101; 64 pregnancies with 37 censored observations) from 14 to 20 days postpartum, compared with cows with RFM, twins, or both that received no treatment (control group; 106; 56 pregnancies with 50 censored observations).

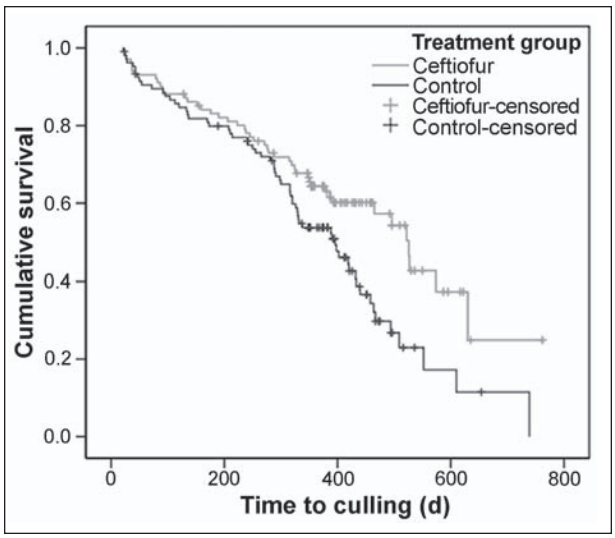

Figure 2—Kaplan-Meier survival curves for analysis of time to culling in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101; 45 culling events with 56 censored observations) from 14 to 20 days postpartum, compared with cows with RFM, twins, or both that received no treatment (control group; 106; 65 culling events with 41 censored observations).

variable logistic regression model. All categorical variables were recoded as indicator variables. To build the models, the treatment variable was forced into the model along with lactation age (categorized into 1, 2, 3, and 4+ lactation levels), and subsequent covariates were analyzed by use of the forward stepwise procedure with entry criteria set at $P < 0.05$ and exit criteria set at $P > 0.10$. The *P* value for the treatment term is given for all outcomes. For all analyses, values of $P < 0.05$ were considered significant.

The covariate-adjusted effect of treatment on the time to event variables was assessed in a Cox proportional hazards model with categorical variables coded into indicator variables. The model building procedure followed that described for the logistic regression model. For the time to pregnancy analysis, data were censored because of culling or death; for the time from calving to culling analysis, data were censored because of death (rarely) or because the cow entered the subsequent lactation (most often).

For the prospective cohort study, descriptive statistics, bivariate analyses, and multivariable models were constructed as described for the single-blind randomized clinical trial.

Results

A total of 2,808 records were initially included in the study. During the study, 146 cases of RFM (5.2 events/100 calvings) and 126 cases of twins were recorded (4.5 events/100 calvings); 12 of those calvings had both RFM and twins. Of the 2,808 cows overall, 53 cows with RFM/T were excluded from the study because weekly scheduling difficulties precluded proper treatment allocation. In addition, 117 records were excluded for those cows leaving the herd prior to 21 days in lactation. One hundred ninety-six records representing the second recorded calving event during the study were excluded (none from the clinical trial). Therefore, 2,442 records were used in the study analyses; 207 cows were enrolled in the clinical trial (101 in the ceftiofur group and 106 in the control group), whereas 2,235 cows were included in the referent group (**Table 1**). The unadjusted risk of subsequent calving in the herd, culling, and reproductive culling differed significantly ($P < 0.05$) between control and ceftiofur groups; cows in the ceftiofur group had a lower overall risk of culling, a lower reproductive risk of culling (44.6% vs 61.3% and 14.9% vs 32.1%, respectively), and an increased probability of a subsequent lactation in the herd (50.5% vs 34.0%), compared with the control group.

Table 2—Frequencies (percentage) for each of the categorical explanatory variables considered as potential confounders or effect modifiers when assessing the effects of treatment in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group) from 14 to 20 days after parturition, compared with cows with RFM, twins, or both that received no treatment (control group) or cows that calved but did not have RFM or twins (referent group).

		RFM, twins, or both (Stratified by treatment)					
Covariate	Covariate levels	Control (n = 106)	Ceftiofur (101)*	*P* value†	Referent (2,235)*	*P* value‡	Total (2,442)
Lactation	1	30 (28.3)	25 (24.8)	0.453	1,141 (51.1)	< 0.001	1,196 (49.0)
	2	32 (30.2)	35 (34.7)		490 (21.9)		557 (22.8)
	3	24 (22.6)	16 (15.8)		193 (13.1)		333 (13.6)
	4+	20 (18.9)	25 (24.8)		311 (13.9)		356 (14.6)
Stillborn calf (or calves)	No	84 (79.2)	82 (81.2)	0.726	2,059 (92.1)	< 0.001	2,225 (91.1)
	Yes	22 (20.8)	19 (18.8)		176 (7.9)		217 (8.9)
Twins	No	57 (53.8)	50 (49.5)	0.539	2,235 (100.0)	NA	2,342 (95.9)
	Yes	49 (46.2)	51 (50.5)		0 (0.0)		100 (4.1)
RFM	No	46 (43.4)	45 (44.6)	0.867	2,235 (100.0)	NA	2,326 (95.2)
	Yes	60 (56.6)	56 (55.4)		0 (0.0)		116 (4.8)
Pyrexia	No	43 (40.6)	44 (43.6)	0.662	1,410 (63.1)	< 0.001	1,497 (61.3)
	Yes	63 (59.4)	57 (56.4)		825 (36.9)		945 (38.7)
Metritis	No	93 (87.7)	94 (93.1)	0.194	2,194 (98.2)	< 0.001	2,381 (97.5)
	Yes	13 (12.3)	7 (6.9)		41 (1.8)		61 (2.5)
Ketosis	No	100 (94.3)	95 (94.1)	0.931	2,158 (96.6)	0.185	2,353 (96.4)
	Yes	6 (5.7)	6 (5.9)		77 (3.4)		89 (3.6)
First case of mastitis	No	90 (84.9)	83 (82.2)	0.597	1,875 (83.9)	0.647	2,048 (83.9)
	Yes	16 (15.1)	18 (17.8)		360 (16.1)		394 (16.1)
Second case of mastitis	No	104 (98.1)	98 (97.0)	0.612	2,189 (97.9)	0.532	2,391 (97.9)
	Yes	2 (1.9)	3 (3.0)		46 (2.1)		51 (2.1)
Displaced abomasum (left or right)	No	103 (97.2)	93 (92.1)	0.103	2,170 (97.1)	0.005	2,366 (96.9)
	Yes	3 (2.8)	8 (7.9)		65 (2.9)		76 (3.1)
Bovine parturient paresis	No	106 (100.0)	100 (99.0)	0.304	2,230 (99.8)	0.137	2,436 (99.8)
	Yes	0 (0.0)	1 (1.0)		5 (0.2)		6 (0.2)
Lameness	No	100 (94.3)	96 (95.0)	0.820	2,126 (95.1)	0.973	2,222 (95.1)
	Yes	6 (5.7)	5 (5.0)		109 (4.9)		114 (4.9)
Diarrhea	No	93 (87.7)	90 (89.1)	0.758	2,096 (93.8)	0.061	2,279 (93.3)
	Yes	13 (12.3)	11 (10.9)		139 (6.2)		163 (6.7)

*Those column subtotals that are not equal to the total number of cows in a given stratum have missing values for the covariate; percentages sum to 100%. †*P* values were derived from an asymptotic Pearson χ^2 2-sided test of association (unadjusted) comparing cows in the ceftiofur group with cows in the control group. ‡*P* values were derived from an asymptotic Pearson χ^2 2-sided test of association (unadjusted) comparing cows in the ceftiofur group with cows in the referent group. No appropriate comparison is possible for either the risk of twinning or risk of RFM in the referent group (having been defined as not present).

NA = Not applicable.

There were no significant differences in the unadjusted risks for confirmed pregnancy (overall and TAI) or death. Comparing the ceftiofur group to the referent group, the only significant ($P < 0.05$) risk differences (unadjusted) were for a confirmed pregnancy from any insemination (73.7% vs 63.4%, respectively). The mean ± SE number of days cows were not in lactation during the previous lactation was 63.75 ± 0.376 days. The mean ± SE age of cows (in days) was 1,206 ± 10.9 days, and the mean ± SE lactation age was 2.03 ± 0.027.

For the single-blind randomized clinical trial, results of the unadjusted nonparametric Kaplan-Meier model for time to pregnancy indicated that the decrease in the

Table 3—Results of the final multivariable logistic regression models for the risk of confirmed pregnancy from all inseminations in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101) from 14 to 20 days after parturition, compared with cows with RFM, twins, or both that received no treatment (model I; control group; 106) or cows that calved but did not have RFM or twins (model II; referent group; 2,235).

Explanatory variable	Overall *P* value	Level of variable	b	SE (b)	*P* value	OR	95% CI
Model I							
Intercept	0.017	NA	0.799	0.334	0.017	2.22	NA
Treatment	0.080	Control	NA	NA	NA	NA	NA
		Ceftiofur	0.523	0.299	0.080	1.69	0.94, 3.03
Lactation age	0.071	1	NA	NA	NA	NA	NA
		2	–0.697	0.403	0.084	0.50	0.23, 1.10
		3	–0.651	0.449	0.147	0.52	0.22, 1.26
		4+	–1.150	0.437	0.009	0.32	0.13, 0.75
Ketosis	0.008	No	NA	NA	NA	NA	NA
		Yes	–2.104	0.796	0.008	0.12	0.03, 0.58
Model II							
Intercept	< 0.001	NA	1.543	0.089	< 0.001	4.681	NA
Cohort	0.394	Referent	NA	NA	NA	NA	NA
		Ceftiofur	–0.187	0.220	0.394	0.83	0.49, 1.16
Lactation age	< 0.001	1	NA	NA	NA	NA	NA
		2	–0.558	0.123	< 0.001	0.57	0.45, 0.73
		3	–0.462	0.148	0.002	0.63	0.47, 0.84
		4+	–0.891	0.138	< 0.001	0.41	0.31, 0.54
Displaced abomasum (left or right)	< 0.001	No	NA	NA	NA	NA	NA
		Yes	–1.070	0.244	< 0.001	0.34	0.21, 0.55
Pyrexia	< 0.001	No	NA	NA	NA	NA	NA
		Yes	–0.380	0.100	< 0.001	0.68	0.56, 0.83

Overall *P* value = Global test of significance of all levels of affiliated indicator variables. b = Parameter estimate. OR = Odds ratio. CI = Confidence interval.
See Table 2 for remainder of key.

Table 4—Results of the final multivariable logistic regression models for the risk of culling (all causes) during a lactation in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101) from 14 to 20 days after parturition, compared with cows with RFM, twins, or both that received no treatment (model I; control group; 106) or cows that calved but did not have RFM or twins (model II; referent group; 2,235).

Explanatory variable	Overall *P* value	Level of variable	b	SE (b)	*P* value	OR	95% CI
Model I							
Intercept	0.873	NA	0.050	0.312	0.873	1.05	NA
Treatment	0.013	Control	NA	NA	NA	NA	NA
		Ceftiofur	–0.734	0.294	0.013	0.48	0.27, 0.85
Lactation age	0.254	1	NA	NA	NA	NA	NA
		2	0.203	0.383	0.597	1.23	0.58, 2.59
		3	0.506	0.432	0.241	1.66	0.71, 3.87
		4+	0.796	0.425	0.061	2.22	0.96, 5.10
Ketosis	0.020	No	NA	NA	NA	NA	NA
		Yes	2.472	1.065	0.020	9.94	1.23, 80.15
Model II							
Intercept	< 0.0001	NA	–1.022	0.080	< 0.001	0.360	NA
Cohort	0.954	Referent	NA	NA	NA	NA	NA
		Ceftiofur	–0.012	0.213	0.954	0.988	0.65, 1.50
Lactation age	< 0.0001	1	NA	NA	NA	NA	NA
		2	0.532	0.113	< 0.001	1.70	1.37, 2.12
		3	0.582	0.135	< 0.001	1.79	1.37, 2.33
		4+	0.918	0.130	< 0.001	2.50	1.94, 3.23
Stillborn calf (or calves)	0.029	No	NA	NA	NA	NA	NA
		Yes	0.371	0.156	0.017	1.45	1.07, 1.97
Pyrexia	0.003	No	NA	NA	NA	NA	NA
		Yes	0.283	0.093	0.002	1.33	1.11, 1.59
Displaced abomasum (left or right)	0.005	No	NA	NA	NA	NA	NA
		Yes	0.963	0.251	< 0.001	2.62	1.60, 4.29

See Table 3 for key.

median time to pregnancy for cows in the ceftiofur group (165 days) was not significantly different from that for cows in the control group (210 days; log-rank test, $P = 0.245$; **Figure 1**). On the other hand, the within-lactation median time to culling differed significantly (log-rank test, $P = 0.011$; unadjusted nonparametric survival analysis) between the ceftiofur group (526 days) and the control group (396 days; **Figure 2**). The cohort study survival curves for ceftiofur-group cows versus referent-group cows compared time to pregnancy and time to culling, respectively (**Figures 3 and 4**). Neither of these outcomes differed significantly using the log-rank test.

Categorical variables with the potential to confound the association between the treatment and out-

Table 5—Results of the final multivariable Cox regression models of time to pregnancy in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101) from 14 to 20 days after parturition, compared with cows with RFM, twins, or both that received no treatment (model I; control group; 106) or cows that calved but did not have RFM or twins (model II; referent group; 2,235).

Explanatory variable	Overall *P* value	Level of variable	b	SE (b)	*P* value	HR	95% CI
Model I							
Treatment	0.108	Control	NA	NA	NA	NA	NA
		Ceftiofur	0.300	0.186	0.108	1.35	0.94, 1.95
Lactation age	0.062	1	NA	NA	NA	NA	NA
		2	–0.503	0.233	0.031	0.605	0.38, 0.96
		3	–0.213	0.264	0.420	0.808	0.48, 1.36
		4+	–0.645	0.276	0.019	0.525	0.31, 0.90
Ketosis	0.017	No	NA	NA	NA	NA	NA
		Yes	–1.709	0.716	0.017	0.181	0.05, 0.74
Model II							
Cohort	0.443	Referent	NA	NA	NA	NA	NA
		Ceftiofur	0.100	0.130	0.443	1.11	0.86, 1.43
Lactation age	0.026	1	NA	NA	NA	NA	NA
		2	–0.083	0.064	0.190	0.92	0.81, 1.05
		3	–0.022	0.076	0.770	0.98	0.84, 1.14
		4+	–0.230	0.078	0.003	0.79	0.68, 0.93
Stillborn calf (or calves)	0.038	No	NA	NA	NA	NA	NA
		Yes	–0.188	0.091	0.038	0.83	0.69, 0.99
Pyrexia	0.032	No	NA	NA	NA	NA	NA
		Yes	–0.111	0.052	0.032	0.90	0.81, 0.99
Displaced abomasum (left or right)	0.022	No	NA	NA	NA	NA	NA
		Yes	–0.399	0.174	0.022	0.67	0.48, 0.94

HR = Hazard ratio.
Model I included 120 pregnancies and 87 censored observations; model II included 1,711 pregnancies and 625 censored observations.
See Table 3 for remainder of key.

Table 6—Results of the final multivariable Cox regression models of time to culling in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101) from 14 to 20 days after parturition, compared with cows with RFM, twins, or both that received no treatment (model I; control group; 106) or cows that calved but did not have RFM or twins (model II; referent group; 2,235).

Explanatory variable	Overall *P* value	Level of variable	b	SE (b)	*P* value	HR	95% CI
Model I							
Treatment	0.011	Control	NA	NA	NA	NA	NA
		Ceftiofur	–0.504	0.199	0.011	0.60	0.41, 0.89
Lactation	0.100	1	NA	NA	NA	NA	NA
		2	0.141	0.267	0.596	1.15	0.68, 1.94
		3	0.602	0.294	0.041	1.83	1.03, 3.25
		4+	0.519	0.280	0.063	1.68	0.97, 2.91
Ketosis	0.008	No	NA	NA	NA	NA	NA
		Yes	0.855	0.324	0.008	2.35	1.25, 4.44
Model II							
Cohort	0.890	Referent	NA	NA	NA	NA	NA
		Ceftiofur	0.022	0.156	0.890	1.02	0.75, 1.32
Lactation	< 0.0001	1	NA	NA	NA	NA	NA
		2	0.500	0.089	< 0.001	1.65	1.39, 1.96
		3	0.479	0.103	< 0.001	1.62	1.32, 1.98
		4+	0.740	0.096	< 0.001	2.10	1.73, 2.53
Pyrexia	0.002	No	NA	NA	NA	NA	NA
		Yes	0.221	0.071	0.002	1.25	1.09, 1.43
First case of mastitis	< 0.001	No	NA	NA	NA	NA	NA
		Yes	0.425	0.082	< 0.001	1.53	1.30, 1.80
Displaced abomasum (left or right)	< 0.001	No	NA	NA	NA	NA	NA
		Yes	0.677	0.154	< 0. 001	1.97	1.46, 2.66
Lameness	< 0.001	No	NA	NA	NA	NA	NA
		Yes	0.526	0.135	< 0.001	1.69	1.30, 2.20

Model I included 110 culling events and 97 censored observations; model II included 877 culling events and 1,459 censored observations.
See Tables 3 and 5 for remainder of key.

comes were evenly distributed ($P > 0.10$) among the ceftiofur and control groups (**Table 2**). However, cows were generally younger, and the risks of stillborn calf, pyrexia, metritis, and displaced abomasum were uniformly lower ($P < 0.05$) among cows in the referent group, compared with cows in the ceftiofur group (Table 2). The continuous covariates, number of days cows were not in lactation during the previous lactation ($P = 0.820$), age of cows in days ($P = 0.283$), and lactation age ($P = 0.359$) were equitably distributed among treatment groups as determined by a 2-sided *t* test.

Results of the final multivariable logistic regression models for number of cows confirmed pregnant at the first TAI (adjusted **odds ratio [OR]**, 1.93; $P = 0.125$) and number of cows confirmed pregnant from any insemination (adjusted OR, 1.66; $P = 0.081$) indicated that use of ceftiofur did not significantly increase the probability of conception when adjusted for lactation age (**Table 3**). Results of the final model for calving in the herd at a subsequent lactation indicated a significant (adjusted OR, 2.10; $P = 0.011$) improvement in the ceftiofur group when adjusted for lactation age. However, this outcome was largely dependent on the differences in the number of cows culled between the control and the treatment groups.

Results of the final multivariable logistic regression models indicated that cows in the control group were at a significantly ($P < 0.05$) higher risk of being culled in each lactation when adjusted for lactation age and ketosis, compared with cows in the ceftiofur group. The overall risk of culling was decreased (adjusted OR, 0.48; $P = 0.013$) in cows in the ceftiofur group, compared with cows in the control group (**Table 4**). The cause-specific risk of culling associated with reproductive reasons (as coded and including abortions) was significantly decreased (adjusted OR, 0.42; $P = 0.032$) in cows in the ceftiofur group.

In the final multivariable Cox regression survival model for time to pregnancy, results for the **hazard ratio** (adjusted **HR**, 1.35) comparing cows in the ceftiofur group with cows in the control group indicated that the increase in the hazard of pregnancy, adjusted for lactation age and ketosis event, was not significantly different between groups ($P = 0.108$; **Table 5**). Results of time to culling differed from that of time to pregnancy in multivariable Cox regression modeling; when adjusted for lactation age and ketosis event, cows in the ceftiofur group remained in the herd longer (adjusted HR, 0.60; $P = 0.011$) than cows in the control group (**Table 6**).

Prospective cohort study—Results of the multivariable logistic regression model suggested that the risk of pregnancy in cows in the ceftiofur group did not differ significantly from that in cows in the referent group (adjusted OR, 0.83; $P = 0.394$; Table 3). This final model was adjusted for age (lactation number), displaced abomasum, and pyrexia. The final multivariable adjusted model for risk of culling was adjusted for lactation, stillborn calf, pyrexia, and displaced abomasum as explanatory variables (Table 4). The risk of culling for cows in the ceftiofur group was not different from that in cows in the referent group (adjusted OR, 0.988; $P = 0.954$).

The final Cox multivariable regression survival model for time to pregnancy indicated that there was no difference in the hazard for pregnancy between the ceftiofur and referent groups (adjusted HR, 1.11; $P = 0.443$; Table 5). Results of the final Cox regression survival model for time to culling indicated that lactation age, pyrexia, first case of mastitis, displaced abomasum, and lameness significantly increased the hazard for culling. After adjusting for these factors, there was no difference in the hazard for culling between the ceftiofur and referent groups (adjusted HR, 1.02; $P = 0.890$; Table 6).

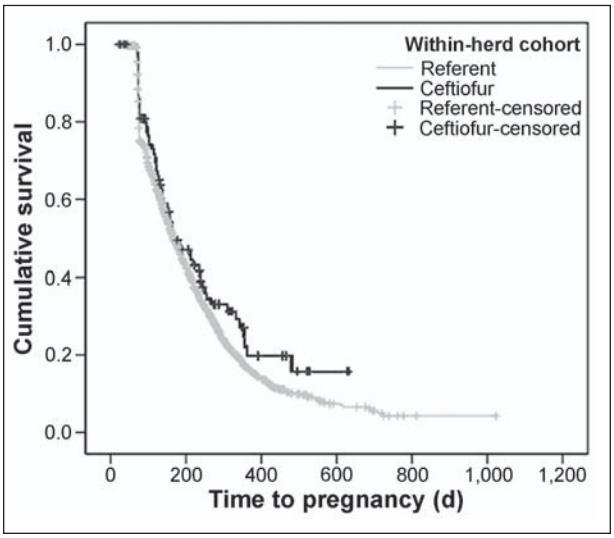

Figure 3—Kaplan-Meier survival curves for analysis of time to pregnancy in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101; 64 pregnancies with 37 censored observations) from 14 to 20 days postpartum, compared with cows that calved but did not have RFM or twins (referent group; 2,235; 1,647 pregnancies with 588 censored observations).

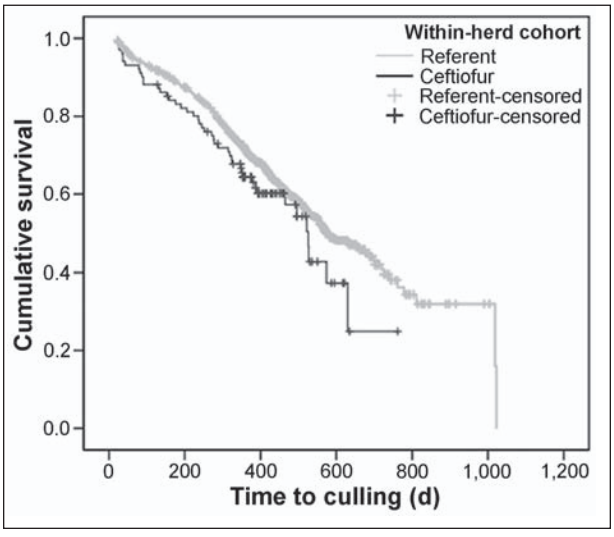

Figure 4—Kaplan-Meier survival curves for the analysis of time to culling in cows with RFM, twins, or both that were treated with a single intrauterine administration of ceftiofur sodium (1 g in 20 mL of sterile water; ceftiofur group; n = 101; 45 culling events with 56 censored observations) from 14 to 20 days postpartum, compared with cows that calved but did not have RFM or twins (referent group; 2,235; 832 culling events with 1,403 censored observations).

Discussion

In the study reported here, the recorded incidence of stillborn calves, twins, RFM, and various health problems (pyrexia, metritis, bovine parturient paresis, first and second cases of mastitis, ketosis, displaced abomasum, lameness, and diarrhea) was similar to those reported in the literature with a few exceptions. The overall incidence of 5.2 RFM/100 calvings (including cows culled < 21 days postpartum) was lower than that previously reported for this herd[2] and in other studies.[4,14] After quantification of the negative effect of RFM on reproductive success in the previous study,[2] the management techniques detailed in the Materials and Methods were implemented to decrease the incidence of RFM; however, 5% of cows continued to have RFM. A twinning rate of 4.5% (including cows culled < 21 days after parturition) is in the range of that reported by Kinsel et al[6] (2.4%) in 1998 and Johanson et al[5] (5.5%) in 2001.

In 2003, Risco and Hernandez[15] reported that the proportion of cows developing metritis after having RFM was significantly decreased from 42% to 13% by ceftiofur hydrochloride administered IM, compared with cows receiving ECP or those that were not treated. In that study, although cows with RFM that were treated with ECP were less likely to conceive than untreated control cows, comparisons to cows without RFM were not made and reproductive performance data were truncated at a maximum of 200 days in lactation. In the study reported here, there was no significant difference in the number of cows with pyrexia within 10 days after parturition or in the incidence of metritis between control and ceftiofur groups. Because all cows on this trial had their rectal temperature monitored for 10 days after parturition and any cow with a rectal temperature > 39.5°C was treated with ceftiofur hydrochloride, differences in the proportion of cows in the ceftiofur and control groups that developed metritis at a later date may have been masked. However, the incidence of metritis and pyrexia in cows in the control and ceftiofur groups was greater than for cows in the referent group, similar to that reported by Risco and Hernandez[15] for cows with RFM that were treated with ceftiofur hydrochloride.

Culling is an important problem in the dairy industry. For the 14,000 herds with 1.7 million cows processed through Dairy Records Management Systems,[b] 34% of the cows leave the herd annually, whereas in herds with ≥ 600 cows, 37% of cows leave the herd annually.[16] Although there was no significant increase in the proportion of cows conceiving at first TAI or from any insemination, fewer cows in the ceftiofur cohort were subsequently culled for reproductive reasons and more cows subsequently calved than in the control group. In 1998, Gröhn et al[4] reported that once conception occurs, the risk of culling markedly decreases, and high milk yield decreases the risk of a cow being culled. In our study, the fact that more cows subsequently calved and fewer were culled for reproductive reasons in the ceftiofur group, compared with the control group, suggested that the cumulative effect of the increase in conception at first TAI, conception at any insemination, and time to pregnancy contributed to the decrease in the number of culled cows in the ceftiofur group and this improved longevity in the herd. Although cows in the control group were culled at significantly higher rates than cows in the ceftiofur group, culling rates for cows in the ceftiofur group did not differ from the rest of the herd (referent group). Therefore, intrauterine treatment with ceftiofur was successful in returning longevity of cows to near normal herd levels, which is important particularly when the value of cows is increasing, milk prices are volatile, and margins are tight, as seen in recent years.[17]

Factors other than ceftiofur treatment that were associated with an increased risk of culling included lactation age, birth of a stillborn calf, pyrexia, displaced abomasum, and lameness. The cause of pyrexia was not determined; however, associated conditions resulting in inappetance may easily have resulted in decreased nutrient availability to support production and reproduction. The other factors that were associated with an increased risk of culling have been reported in the literature to either directly or indirectly affect culling. In a study of diseases affecting culling, Gröhn et al[4] reported that older cows and those with displaced abomasums were at a greater risk of being culled. Fourichon et al[18] reported that locomotor diseases increased the number of days to conception by 12 days and that the estimated effect of stillbirth was low (1.6 days for cows calving without difficulty); therefore, because conception decreases the risk of culling,[4] the negative effect of lameness and stillbirth on fertility could indirectly affect the risk of culling.

Many studies investigating treatments for RFM or metritis have not compared the success of various treatments in cows with RFM or metritis with that in cows without RFM or metritis (referent group) [10,15,19-21] or with cows having RFM or metritis but not receiving any treatment (control group).[10,19] Results of our study suggested that use of ceftiofur as an intrauterine infusion for postparturient cows with RFM/T was effective in increasing the longevity of cows in the herd as measured by the risk of culling and the time to culling. However, intrauterine administration of ceftiofur sodium in cattle is considered extralabel drug use; therefore, the attending veterinarian must follow the AMDUCA guidelines for extralabel drug use and, on the basis of scientific information, determine a withdrawal interval sufficient to preclude violative residues in food and milk. In the single-blind randomized clinical trial, the increases in the proportion of cows confirmed pregnant at first TAI (adjusted OR, 1.69) and hazard for pregnancy (adjusted HR, 1.35) were not significant ($P > 0.05$). Further study to fully assess the efficacy of intrauterine administration of ceftiofur is warranted if the level of improvement reported herein for hazard of pregnancy and success at first TAI are determined to be clinically important. Because cows with rectal temperatures > 39.5°C during the first 10 days after parturition were treated with ceftiofur hydrochloride IM, the power of the statistical analyses to detect differences may have been diminished. Therefore, future studies evaluating intrauterine administration of ceftiofur sodium and use of ceftiofur hydrochloride for treatment of pyrexia could incorporate a 2 × 2 factorial design to assess both treatments simultaneously.

a. Texas Dairy Herd Improvement Association, College Station, Tex.
b. DairyComp 305, Valley Agricultural Software, Tulare, Calif.
c. National Association of Animal Breeders, Columbia, Mo.
d. Estradiol cypionate, Pfizer Animal Health Inc, New York, NY.
e. Excenel RTU sterile suspension, Pfizer Animal Health Inc, New York, NY.
f. Naxcel, Pfizer Animal Health Inc, New York, NY.
g. SPSS, version 11.5 for Windows, Chicago, Ill.

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