Effect of administration of a controlled-release monensin capsule on incidence of calving-related disorders, fertility, and milk yield in dairy cows

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Objective—To determine the effect of a controlled-release monensin capsule administered at cessation of lactation on incidence of calving-related disorders, fertility, and milk yield in dairy cows.

Animals—290 dairy cows treated with monensin and 290 untreated control cows.

Procedure—Treated cows received a capsule that released monensin at 335 mg/d for 95 days. Incidence of calving-related disorders; daily milk yield up to 20 days postpartum; test-day milk yield, fat, protein, and mature-equivalent 305-day milk production; and body condition score at calving were determined. Reproductive variables were conception rate at first service, pregnancy rate, and calving-to-conception interval.

Results—Cows treated with monensin were 2.1 times as likely to develop dystocia and 0.8 times as likely to develop metritis as control cows. For milk yield, there was an interaction of treatment X time X parity. In multiparous cows, monensin significantly improved milk yield at test days 4 and 7. In addition, monensin increased body condition score at calving.

Conclusions and Clinical Relevance—Despite increasing the likelihood of developing dystocia and metritis, administration of monensin improved the lactational performance of multiparous cows and may be a promising additive for use at the time of cessation of lactation. (*Am J Vet Res* 2006;67:537–543)

The transition period in dairy cows is defined as 3 weeks before and 3 weeks after parturition and is characterized by tremendous physiologic and metabolic demands. Calving is a major component of this stage[1]; consequently, calving-related disorders, such as hypocalcemia, retained fetal membranes, metritis, fatty liver, ketosis, left and right displacement of the abomasum, mastitis, and lameness, are common conditions that have a negative economic impact on dairy herds.[2] The negative impact of calving-related disorders on reproductive performance and milk production has been well documented.[3] Therefore, any successful attempt to decrease the incidence of calving-related disorders will positively affect milk yield and fertility in dairy cows.

Monensin is an ionophore that affects rumen fermentation dynamics.[4] The most consistent and well-documented fermentation alteration is increased proportion of propionic acid with a concurrent decrease in the proportion of acetate and butyrate.[5] As a result, a lower incidence of ketosis and lipid mobilization–related disorders has been achieved.[6,7]

Monensin has been available for use in food animals for more than 20 years. However, limited information is available about its effect in lactating dairy cows. During the past 7 years, several research studies[8-12] have been conducted in Canada and Australia on the use of monensin in the form of a controlled-release capsule. Monensin has recently been approved for use in lactating dairy cattle in the United States. We hypothesized that treatment with monensin in Holstein cows during use of typical Florida diets would be associated with a decrease in the incidence of calving-related disorders and an increase in milk production.

The purpose of the study reported here was to determine the effect of a controlled-release monensin capsule administered at cessation of lactation on the incidence of calving-related disorders, fertility, and milk yield during the transition period in dairy cows.

Materials and Methods

Cows and herd management—This study was approved by the Institutional Animal Care and Use Committee of the University of Florida, and use of the monensin controlled-release capsule was approved by the US FDA (INAD No. 10749). The study was conducted on a commercial dairy farm with 3,000 milking cows that were located in north-central Florida. Cows had a 305-day mean mature-equivalent milk production of 10,700 kg. Lactating cows were housed in a drylot system and were fed the same total mixed ration 3 times/d to meet or exceed the nutritional requirements of the National Research Council.[13] Postpartum transition cows received a diet higher in neutral detergent fiber (**Tables 1 and 2**). Cows were managed to cease lactation from 50 to 70 days before expected parturition, housed in a drylot, and fed a diet typical for nonlactating Florida cows. At 21 days before expected parturition, dry cows were moved from the drylot to a different prepartum drylot and were considered to be prepartum transition cows. Twice per day, they were fed a diet with a dietary cation anion difference

DHIA Dairy Herd Improvement Association

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of –51.7 mEq/kg (dry matter basis) by use of the following equation:

$$\text{Dietary cation anion difference (mEq)} = (Na^+ + K^+) - (Cl^- + S^-)$$

Cows calved in the drylot, and the calf was immediately separated from the dam at parturition. If the cow needed calving assistance, it was moved to a maternity barn. Cows were processed within 12 hours postpartum by use of a routine that included recording body condition score, udder score (for edema), reproductive tract status (trauma or lacerations), and whether the cow was suspected of having retained fetal membranes. If cows developed either retained fetal membranes or hypocalcemia, they were treated and remained in the hospital barn until recovery. After processing, cows were moved to a postpartum lot and fed a lactation diet high in forage neutral detergent fiber (Tables 1 and 2). Within 21 days postpartum (now considered postpartum transition cows), cows were monitored daily on the basis of their milk yield for the development of metritis, ketosis, and displacement of the abomasum. Any condition was recorded and treated accordingly.

Beginning 60 days postpartum, cows received bovine somatotropin[a] SC every 14 days during the entire lactation. Reproductive management included a waiting period of 80 days until first insemination. First service was synchronized and used a timed artificial insemination protocol. Thereafter, cows were identified as being in estrus by use of visual observation or a computerized pedometer system[b] and inseminated at estrus. Pregnancy diagnosis was performed by herd veterinarians via palpation per rectum of the uterus and its contents at approximately 42 to 49 days after insemination. Lactating cows were tested for milk yield, milk solids, and somatic cell count once per month by the DHIA.[c]

Experimental protocol—During July to August 2001, 580 cows at 50 to 70 days before expected parturition were

Table 1—Composition of diets fed to prepartum and lactating dairy cows during 3 periods.

Feed component	Prepartum period[a]	Prepartum transition period[b]	Lactating transition period[c]
Alfalfa hay	0	19.3	17.53
Coastal hay	0	4.76	0
Cottonseed (whole)	0	9.84	8.75
Corn silage	44.90	24.06	28.50
Ryegrass silage	15.29	0	4.20
Corn hominy	0	6.98	13.54
Citrus pulp	21.20	9.82	4.25
Soybean meal	17.20	3.44	5.49
Wet brewer's grain	0	10.74	4.07
Lactating concentrate	0	0	7.03
Lactowhey*	0	3.76	4.23
Energy supplement†	0	2.79	1.96
Springer minerals‡	0	4.51	0
Nonlactating cow minerals	1.41	0	0
Lactating cow minerals	0	0	0.45

Values are percentage of diet on a dry matter basis.
*Ammoniated whey (61.5% crude protein). †Energy supplement based on sodium propionate, propylene glycol, dried whey, and calcium carbonate. ‡Springer minerals are minerals given for approximately 21 days before parturition.
[a]70 to 21 days before expected parturition. [b]21 days before expected parturition to calving. [c]Calving to 21 days postpartum.

Table 2—Nutrient content of diets fed to prepartum and lactating dairy cows during 3 periods.

Nutrient	Prepartum period[a]	Prepartum transition period[b]	Lactating transition period[c]
CP (DM)*	15.52	17.91	18.60
Undegradable protein (% CP)†	26.38	35.31	30.34
Degradable protein (% CP)‡	73.62	64.69	69.66
Soluble protein (% CP)‡	unknown	36.72	39.77
Net energy lactation (Mcal/kg)§	0.84	1.69	1.69
Acid detergent fiber (% DM)*	24.54	25.13	23.66
Neutral detergent fiber (% DM)*	36.04	36.20	34.63
Nonfiber carbohydrates (% DM)†	32.94	31.55	34.13
Starch (% DM)†	11.05	14.96	14.90
Lipid (% DM)*	2.85	6.20	2.36
Ca (% DM)*	0.74	1.27	1.10
P (% DM)*	0.30	0.35	0.46
Mg (% DM)*	0.32	0.36	0.36
K (% DM)*	1.28	1.10	1.46
Na (% DM)*	0.09	0.09	0.58
Cl (% DM)*	0.18	0.43	0.48
S (% DM)*	0.24	0.4	0.22
Forage in diet (% DM)	60.21	48.10	50.23
Dietary cation-anion difference (mEq/kg [DM])§	165.9	–51.7	351.9

*Laboratory nutritional analysis. †Values from feed composition tables. ‡From formulas after laboratory analysis. §From formula $(Na^+ + K^+) - (Cl^- + S^-)$.
CP = crude protein. DM = Dry matter.

randomly assigned to either a treatment or control group. The treated group (n = 290) received orally a capsule of monensin[d] designed to remain in the rumen and release 335 mg of monesin daily for 95 days. Control cows (no capsule; n = 290) were randomly matched by parity (1, 2, and ≥ 3) and categorized as primiparous (parity 1) and multiparous (parity ≥ 2). The number of animals per treatment was calculated with the expectation of a reduction in the incidence of retained fetal membranes or metritis of 6% (95% confidence; 80% power).[14]

Outcome variables and case definitions—Outcome variables were the incidence of dystocia, clinical hypocalcemia, retained fetal membranes, metritis, clinical ketosis, displacement of the abomasum, and culling rate. Incidence was defined as the number of specified new cases during the lactation period of risk for that condition divided by the total number of cows in that group. Case definitions were mainly based on a previous report by Kelton et al.[2] Dystocia was defined as human intervention (2 or more people) involving forced extraction of the calf.[3] Hypocalcemia was diagnosed in any cow detected within 72 hours after parturition with anorexia, CNS signs, staggering, various degrees of unconsciousness, and good response to IV administration of calcium. Retained fetal membranes were defined as visible fetal membranes at the vulva, vagina, or uterus as detected via physical examination more than 24 hours after calving. Metritis was defined as any abnormal vaginal discharge or uterine content (foul smelling) obtained via rectal palpation.[2,3] Ketosis was defined as a decrease in milk production and high concentration of urine ketones (> 40 mg/dL), as measured with a commercial test that has moderate sensitivity and high specificity.[e] Displacement of the abomasum was defined as decreased milk yield accompanied by an audible high-pitched tympanic resonance elicited by percussion of the left or right abdominal wall between the 9th and 12th rib spaces, with or without colic pain and confirmed via surgical intervention. Culling rate was defined as the number of cows that were removed from the herd for any reason before 410 days postpartum divided by the number of cows that were enrolled in the trial. Other outcome variables were daily milk yield up to 20 days postpartum and milk production, milk fat, and protein content at the first 10 DHIA test days during lactation. Mature-equivalent 305-day milk production was also recorded on the basis of DHIA information. Body condition score was determined at assignment, calving, and 60 days postpartum, according to a standard methodology[15] and by the same person.

Reproductive variables used to evaluate fertility were conception rate at first service, pregnancy rate, and calving-to-conception interval. Conception rate at first service was defined as the number of cows pregnant at their first service divided by the number of cows inseminated for the first time after calving. Pregnancy rate was defined as the number of cows that became pregnant up to 410 days of lactation divided by the number of cows inseminated at least once during that period. Calving-to-conception interval was defined as the mean days between calving and the breeding date at which cows were confirmed pregnant.

Statistical analysis—The null hypothesis was that there was no difference in the incidence of calving-related disorders and other outcomes between groups. Incidences of calving-related disorders were analyzed by use of logistic regression, corrected for parity (primiparous or multiparous) and body condition score at calving (≥ 3.25 or < 3.25). Models for retained fetal membranes and metritis were additionally corrected for dystocia. A backward-elimination procedure was conducted for each model. Treatment was forced into the final models. To determine the degree of association between risk factors and outcome variables, odd ratios and 95% confidence intervals were calculated. Milk yield was analyzed by constructing a mixed model for repeated measures. Body condition score at assignment was included as a covariate in the model. A triple-interaction effect of treatment × test day × parity was conducted to test the parallelism of milk curves. Body condition score at calving was analyzed by use of the Wilcoxon rank test within parity (Shapiro-Wilk test; $P < 0.01$) and by use of ANOVA for testing the interaction of treatment × parity. Overall pregnancy rate was analyzed by use of survival analysis. Conception rate at first service was analyzed by use of logistic regression as described for calving-related disorders. Calving-to-conception interval was analyzed by use of an ANOVA linear model. Differences were considered significant at $P \leq 0.05$. Statistical analyses were conducted by use of the corresponding procedure in a software program.[16] Sample size was calculated by use of software.[f]

Table 3—True incidence (% [nonadjusted]) of calving-related disorders in 290 control cows and 290 cows treated with monensin.

Disorder	Control	Monensin
Dystocia	7.9	30.9*
Hypocalcemia	0.0	0.0
RFM	19.7	22.8
Metritis	42.6	33.8*
Ketosis	2.5	2.8
DA	1.4	0.7
Culling rate	28.6	28.6

*Significant ($P \leq 0.05$) difference from the control group.
RFM = Retained fetal membranes. DA = Displaced abomasum.

Table 4—Summary of logistic regression modeling for calving-related disorders in cows treated with monensin.

Model		Coefficients		
Dependent	Explanatory	OR	95% CI	*P* value
Dystocia	Monensin (yes)	2.10	1.39–3.17	< 0.01
	Parity (primiparous)	0.65	0.43–0.99	0.049
Metritis	Monensin (yes)	0.80	0.70–0.88	< 0.01
	Parity (primiparous)	5.65	3.25–9.82	< 0.01
	Dystocia (yes)	19.2	10.7–38.0	< 0.01

OR = Odds ratio. CI = Confidence interval.

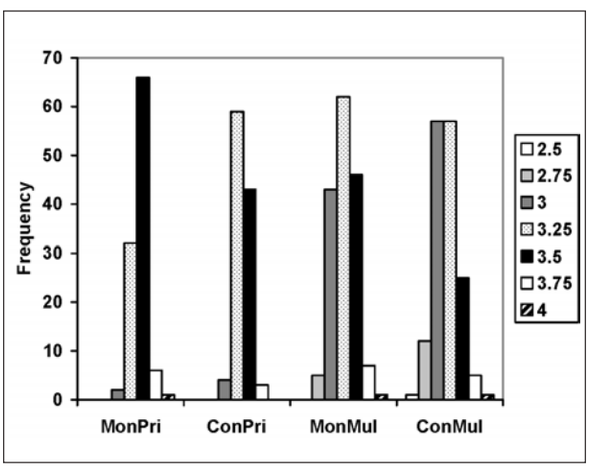

Figure 1—Frequency distribution (No. of cows) for body condition score at calving by treatment and parity in control cows and cows that were treated with monensin. MonPri = Monensin, primiparous. ConPri = Control, primiparous. MonMul = Monensin, multiparous. ConMul = Control, multiparous.

Table 5—Descriptive statistics for body condition score (BCS) at calving by treatment and parity in control cows and cows treated with monensin.

Variable	n	Mean BCS	SEM	Median	Skewness	Kurtosis
Monensin-primiparous	107	3.43*	0.01	3.5	0.05	1.19
Control-primiparous	109	3.35	0.01	3.25	0.21	–0.16
Monensin-multiparous	164	3.26*	0.01	3.25	0.14	–0.22
Control-multiparous	158	3.17	0.01	3.25	0.33	0.32

*Significantly ($P = 0.01$) different from matching control group.

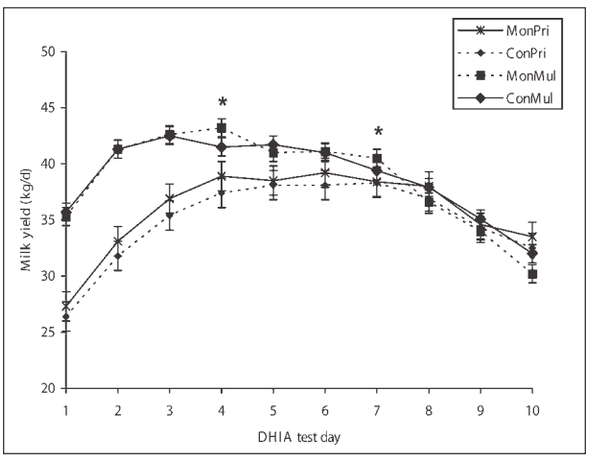

Figure 2—Least squares mean ± SEM test-day milk yield by treatment and parity in control cows and cows treated with monensin. *Significant ($P \leq 0.05$) difference from matching (parity) control group. *See* Figure 1 for key.

Results

The incidences of calving-related disorders and a summary of logistic regression modeling for significant variables were determined (**Tables 3 and 4**). Only dystocia and metritis were affected by treatment. Cows treated with monensin were 2.1 times as likely to develop dystocia as control cows. Correcting for parity and dystocia, treated cows were 0.8 times as likely to develop metritis as control cows. Cows with dystocia and cows in first lactation were, respectively, 19.2 and 5.7 times as likely to develop metritis as cows calving unassisted or older cows.

For body condition score at calving, main effects of parity and treatment were significant. However, the interaction was not significant. Therefore, monensin increased body condition score at calving in both primiparous and multiparous cows (**Figure 1**; **Table 5**).

Daily milk yield up to 20 days postpartum by parity and treatment was not significantly different between treatment groups. Evaluation of the effect of treatment on test-day milk yields for the entire lactation revealed a triple interaction of treatment × parity × test day (**Figure 2**; $P = 0.01$). For primiparous cows, curves of milk production were not significantly different, and for multiparous cows, curves were not parallel; values of test days 4 and 7 were significantly different between treated and control cows. Accumulated milk yields of the entire lactation were not significantly different in cows treated with monensin, compared with controls (mean ± SEM, 13,910 ± 185 kg vs 13,627 ± 185 kg, respectively). Milk fat percentage and milk protein percentage for treated and control cows and within parity were not significantly different over time.

Conception rates at first service were 21.7% and 25.2% for control and treated cows, respectively. Overall pregnancy rates were 53.9% and 58.1% for control and treated cows, respectively. Calving-to-conception interval was 180.2 and 170.4 days (SEM, 12.2 days) for control and treated cows, respectively. For the conception rate at first service and calving-to-conception interval, there was an interaction between treatment and body condition score at 60 days postpartum. Cows treated with monensin were 1.33 times as likely to become pregnant at first service as cows not treated with monensin, although only in cows with a body condition score ≥ 2.75 at 60 days postpartum. Calving-to-conception interval and services per conception were also improved significantly by monensin only in cows with a body condition score ≥ 2.75 at 60 days postpartum. Overall pregnancy rate was not significantly different between treated and control cows.

Discussion

Results of this study partially substantiated our hypothesis because the incidence of some calving-related disorders (dystocia and metritis) was affected by treatment during the transition period. The incidence of clinical hypocalcemia (0%) was consistent with the use of anionic salts in the prepartum period.[17-20] In addition, results regarding clinical hypocalcemia were expected because we assumed that monensin would have no effect on calcium metabolism.

The incidence of retained fetal membranes of approximately 20% was high but consistent with results of a previous study[21] conducted on the same farm and within the range of 1.3% to 39.2% cited in the literature.[2] Perhaps the definition of retained fetal membranes was not consistent and farm personnel misclassified the condition. This might be an overestimation of the true incidence of the disease. The lack of treatment effect was expected because retention of fetal membranes is a multifactorial condition and other variables are more important predisposing factors for retained fetal membranes.[22-24]

The higher incidence of dystocia in older cows treated with monensin, compared with control cows, was unexpected. Although dystocia is also a multifactorial condition, those persons providing calving assistance were unaware of group assignments. An explanation for this finding could be that cows exposed to monensin for a longer period (70 to 50 days) had a significantly higher body condition score at calving than did controls. Therefore, fat deposition may have also occurred inside the pelvis or birth canal, which could

reduce intrapelvic space. Higher body condition score at calving has been associated with a higher incidence of dystocia.[25,26] Another explanation might be that treated cows might have had heavier calves because improved glucose metabolism in the dam may provide more glucose for the developing fetus.[27] Unlike Canadian studies[6,9,11] in which boluses were administered during the last 3 weeks of gestation, boluses were administered 50 to 70 days before expected parturition in the present study, and this may have substantially increased glucose availability for the fetus. In beef cattle, calves from heifers fed monensin had higher birth weights than those from control heifers.[28,29] However, another study[30] found no effect of monensin on calf birth weight. Because this outcome was unexpected, collection of calf birth weight data was not planned or performed.

The incidence of metritis in this study was in the upper portion of the range of values reported in the literature (30% to 40%).[2] This high incidence might be attributable to our less-stringent definition and might be an overestimation of the true incidence. In the present study, abnormal vaginal discharge was used as a criterion. Other studies have used other criteria including body temperature, milk yield, uterine status at palpation, and vaginal discharge.[31] In the present study, monensin treatment was associated with a lower incidence of metritis when corrected for dystocia and parity. This represents a pure effect of treatment on the occurrence of the uterine condition because dystocia and parity were also positively associated with metritis. An explanation for the positive effect of monensin treatment on metritis is speculative. Perhaps treated cows had a better metabolic status postpartum with less fat mobilization and less ketone body production than control cows. This may have allowed for better immune function and prevention of infection, which could lead to metritis. Hyperketonemia impairs chemotaxis, cytokine production, and phagocitic capacity of leukocytes.[32] Indeed, monensin reduces the rate of intramammary infections in lactating dairy cows, suggesting that monensin, through its antiketogenic effect, can decrease immunosuppression in early lactation.[33]

The incidence of clinical ketosis was in the lower portion of the range (2% to 22%) reported by other authors.[2] However, the main criteria used to diagnose ketosis in our trial were a decrease in milk yield and detection of ketone bodies in urine by use of a colorimetric field test based on nitropruside.[e] This might be an underestimation of the real incidence of the disease because the urine test[e] has moderate sensitivity and high specificity.[34] There was no effect of treatment on clinical ketosis, although monensin is antiketogenic in dairy cattle.[6,7,9,35] Most of the Canadian studies have focused on the effects of the bolus on subclinical ketosis rather than clinical ketosis. One of those studies[36] found no difference in the incidence of clinical ketosis between treated and control cows. However, when data from different study populations were pooled to increase sample size, monensin decreased the incidence of clinical ketosis.[36] An explanation for the lack of treatment effect in the present study might be that the transition diet supplied 1.67 Mcal of net energy/kg for lactation and glucose precursors such as milk whey, sodium propionate, and propylene glycol. Perhaps this diet was sufficient to maintain better energy balance, normal glycemia, and a low incidence of clinical ketosis in transition cows, even without monensin treatment.

The incidence of abomasal displacement was in the lower portion of the range of 0.3% to 6.3% reported in the literature.[2] There was no effect of treatment even though control cows had an incidence 2 times that in treated cows. The sample size, relative to the incidence of displacement of abomasum, reduced the power to detect differences attributable to treatment (power, 14%). Similar results were reported in 2 Canadian studies.[7,36] A significant reduction of abomasal displacement associated with monensin as a bolus was found in both studies.

Culling rate was not significantly different between groups. Similar results were reported in a previous review.[37] Overall, culling rate was within the expected range reported in the literature.[38] Clinical hypocalcemia, retained fetal membranes, displacement of abomasum, ketosis, and ovarian cysts significantly affect culling at different stages of lactation. Metritis has no effect on culling.[38] Because the incidences of clinical hypocalcemia, retained fetal membranes, displacement of the abomasum, and clinical ketosis in the present study were similar between treated and control cows, it seemed reasonable that culling rate was similar between groups.

Monensin given at cessation of lactation improved body condition score at calving. Within parity, control and treated cows had similar body condition score at cessation of lactation. However, body condition score was significantly higher in treated than control cows at calving. The effect of monensin as a growth promotant in beef and dairy cows has been described.[30–39] However, in 1 study,[30] dairy heifers treated with monensin did not have alterations in body composition, and in other studies,[9,39,40] cows treated with monensin increased either body weight and body condition score or had reduced body condition score losses after calving. This is in agreement with the present study. Although monensin improved body condition score at calving, this improvement did not cause detrimental effects, other than dystocia, in cows. Another variable not evaluated in the present study that might increase body condition score at calving is the increment of energy density of the diet of nonlactating cows.[13]

In the present study, monensin treatment resulted in a slight nonsignificant increase in milk yield. This finding was consistent with previous studies[10,12,41-44] in which monensin was used as a feed additive (premix) or a controlled-release bolus. Other studies[11,45,46] did not find a positive effect of monensin on milk production. Monensin increased milk yield significantly on the basis of test-day milk yield in multiparous, but not first-lactation, cows. The positive effect of treatment might be explained by the fact that monensin improved body condition score at calving. Indeed, cows with a fair body condition score at calving are higher producers than thin and obese cows.[10] In addition, phenotypic correlations between body condition

score at calving and milk yield are slightly positive in Holstein cows.[47] Monensin did not affect milk solids during the entire lactation. These results are in agreement with some studies[44,46] but not all.[41]

The present study revealed differences in conception rate at first service and calving-to-conception interval between cows with and without monensin and with a body condition score ≥ 2.75 (an interaction effect) at 60 days postpartum. This finding is in agreement with other studies[33,48] that revealed positive effects of monensin on reproductive responses. However, other studies[7,44,49] found no effect of monensin on fertility variables. The fact that the effect of monensin was dependent on body condition score at 60 days postpartum emphasizes the important effects of energy balance and body condition score dynamics during the postpartum period on fertility in dairy cattle. In addition, because the bolus of monensin has a duration of 95 days, the positive effect of the ionophore on fertility could be attributable to improved body condition score at calving in cows treated with monensin during the entire nonlactating period (50 to 70 days prepartum).

a. Posilac, 500-mg sometribove zinc, Monsanto, St Louis, Mo.
b. Afimilk, SAE Afikim, Kibbutz Afikim, Israel.
c. DHIA, Raleigh, NC.
d. CRC Rumensin, Elanco Animal Health, Guelph, ON, Canada.
e. Ketostix, Bayer Corp, Elkhart, Ind.
f. WinEpiscope, version 2.0, software for quantitative veterinary epidemiology. Delphi, version 1.0, Available at: www.clive.ed.ac.uk/winepiscope/. Accessed 2005.

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