Effects of Monensin on the Reproduction, Health, and Milk Production of Dairy Cows

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ABSTRACT

A randomized clinical trial including 1109 cows from 12 Australian dairy herds was used to evaluate the effects of monensin on the health (n = >686 cows), production (n = 915 cows), and reproduction (n = >908 cows) of dairy cows. Cows were allocated to a treatment group receiving a slow-release intraruminal bolus containing 32 g of sodium monensin that was administered 40 d before and 50 d following the anticipated calving date or to a control group. Treatment did not significantly alter any reproductive outcome; 54.5% of cows treated with monensin and 58.2% of control cows were pregnant at first service, and days to conception were lower for cows treated with monensin. The hazard rate (0.95) was not significant for these cows. The percentage of cows pregnant was 83.8 for cows treated with monensin and 83.3 for control cows, and days to first estrus (hazard rate = 1.04) and first service (hazard rate = 1.04) were not significantly higher for treated cows.

Treatment with monensin did not significantly alter the risk of any disease. The incidence of retained fetal membranes, pyometra, lameness, abortion, and infectious diseases was not significantly lower for cows in the treatment group, and the incidence of mastitis was not significantly higher for cows in the treatment group. Monensin significantly increased milk production by 0.75 L/d per cow and tended to increase milk fat and protein yields but had no significant effect on milk fat or milk protein percentages. Changes in the production of milk and milk constituents were consistent throughout lactation.

(Key words: monensin, reproduction, health, milk yield)

INTRODUCTION

Sodium monensin, an ionophore antibiotic produced by Streptomyces cinnaemonensis, selectively modifies the ruminal flora and improves the digestive efficiency of cattle. The effects of monensin supplementation include increased ruminal propionate production (44), reduced in vivo and in vitro production of methane (4), increased DM and starch digestibility (36), decreased production of bacterial protein in the rumen (14, 20), increased nitrogen retention (36), and significantly increased flow of amino acids to the duodenum and digestion of amino acids in the duodenum (20). A decreased ruminal turnover rate and increased rates of ruminal fill have been noted with treatment (36), and monensin can modify the flux of ions across epithelial cells of the intestine and increase the uptake of calcium, selenium, and other cations (8, 12, 39). The treatment of lactating dairy cows with monensin has resulted in increased plasma glucose concentrations (1, 18) and decreased plasma ketone concentrations (1, 35, 40). The capacity of monensin to alter metabolism suggests that the effects of monensin treatment on reproduction, health, and production of dairy cows require further investigation.

Although monensin supplementation modified pituitary and ovarian functions of beef and dairy heifers (28, 32, 33) and cows (31), as evidenced by changes in the luteinizing hormone surge, follicular development, and responses to superovulation, a large, multicenter, randomized trial (23) found that a single monensin bolus administered to dairy cows within 7 d of calving did not significantly alter the interval from calving to conception or conception rate. Similarly, studies of cows on pasture in New Zealand (21) found no significant effect of monensin treatment on reproductive efficiency. Both of those studies
(21, 23) concluded that the treatment protocol used, which might have depressed feed intake shortly after calving (36), might not have been the optimal method to influence fertility. Methods of administering monensin that allow cows to maintain or increase feed intake after calving should increase fertility.

Many costly health disorders that occur in early lactation are associated with increased rates of tissue lipolysis, increased plasma concentrations of ketones, and lower plasma glucose concentrations (3). Each of these metabolic changes has been influenced positively by treatment with monensin (1, 18, 35, 40); the effect of monensin supplementation on the incidence of metabolic disorders of periparturient dairy cows has not been reported. Treatment with monensin, however, decreased the incidence of legume bloat in cattle that grazed pasture dominated by legumes (26) and decreased the risk of lactic acidosis (29). Monensin treatment also has improved neutrophil chemotaxis (40) and may, therefore, reduce the incidence and severity of bacterial disease.

Studies investigating the effects of monensin in dairy cows (23, 26, 43) have not reported a consistent response in either milk production or a change in its constituents. Monensin increases the ratio of propionate to acetate produced in the rumen and should, therefore, produce an increase in lactose and milk production and a decrease in milk fat percentage. The changes in VFA ratios and reduced ruminal degradation of dietary protein (20) observed with monensin treatment may also influence milk protein concentrations.

Monensin can be fed in a sustained-release intraruminal capsule (Rumensin Intra-ruminal Anti-bloat Capsules™; Elanco Animal Health, West Ryde, Sydney, New South Wales, Australia) that releases approximately 300 mg/d of monensin for 100 d (26) and provides a method by which the effects of monensin on cattle reproduction, health, and production may be examined. The objectives of this multiple-center randomized clinical trial were to examine the effects of monensin, administered as an intraruminal bolus 40 d prior to and 50 d following calving, on the health, postpartum reproductive efficiency, and milk production of dairy cows. We postulated that treatment of dairy cows at these times would reduce the risk of postpartum reproductive failure, reduce the incidence of common periparturient clinical disorders, and increase the production of milk and milk solids.

MATERIALS AND METHODS

Herds

Three herds were selected from the Atherton Tablelands, Queensland (QLD), Australia; 7 herds were selected from the Camden district, New South Wales (NSW), Australia; and 2 herds were selected from the Gobburn Valley, Victoria (VIC), Australia. Herds were selected on the basis of good record keeping and regular contact with supervising veterinarians. The herds in QLD and NSW calved year-round, and those from VIC calved seasonally. The use of prostaglandins in the NSW and QLD herds for treatment of reproductive problems was very limited. In the VIC herds, there was limited use of prostaglandin and intravaginal progesterone-releasing devices for synchrony of cows that had not been detected in estrus by the time mating commenced (i.e., mating start date). Farm managers of the NSW and QLD herds did not strictly adhere to a voluntary waiting period, and mating start dates were used in the seasonal calving herds of VIC to establish time of mating. In the VIC herds, bulls were used following 6 wk of artificial insemination. A veterinarian who was unaware of group allocations used palpation to estimate pregnancy dates, and these cows were treated as missing data for first service conception and pregnancy analyses. All herds grazed pasture and were supplemented with grain and other concentrate feeds.

Sample Size

Sample size calculations were based on the determination of a 10% increase in first service conception rate with a Type 1 error (α) of 0.05 and a Type 2 error (β) of 0.10 for a first service conception rate of 65%. A minimum sample size of 450 cows per group was calculated (15). After completion of the study, power calculations on the differences in first service conception rates and milk production among groups were performed using SOLO statistical software (38).

Allocation to Groups

Cows that were due to calve between April 1993 and February 1994 (n = 1109) were allocated to treatment or control groups. Forty-three cows were removed from the trial before the data were pooled, and data from 1066 cows were analyzed. A random numbers table was used to randomize treatment and control groups within all herds, except for 1 herd from QLD and both herds from VIC. For these herds, cows were alternatively assigned to treatment and control groups according to the order in which they were expected to calve. Primiparous cows were not included in this study.

Forty days prior to the anticipated calving date, treated cows were given an intraruminal bolus...
(Rumensin Anti-Bloat Capsule™) that contained 32 g of sodium monensin. Treatment was repeated 50 d after the anticipated calving date. Farm personnel recorded capsule numbers against individual ear tag numbers so that regurgitated capsules could be traced.

Statistical Analysis

The study period was defined as the 300 d following the first treatment of a cow or until cows were removed from the herd. Significance was declared at \( P < 0.05 \) unless otherwise stated.

Reproductive data. The number of days from calving to first observed estrus, first service, and pregnancy were recorded for all herds except for the herds from VIC, for which the date of the first observed estrus was not recorded. Reproductive events were reported for 1056 cows. Seventy-three cows did not have recorded dates for first service and were not pregnant. Of these, 26 were from a single herd in NSW that, during the trial, was divided and moved in part to a separate property. Thirty-three of the 73 cows without a recorded date for first service were allocated to the treatment group, and 40 were controls. These data were treated as missing in the appropriate analyses.

Pregnancy rate (PR) was defined for treatment and control groups as the number of cows that were pregnant divided by the total number of cows that were randomized. First service PR was defined for each group as the number of cows that were pregnant to their first service divided by the total number of cows for which a first service date was recorded. Relative risks (RR) were separately stratified by herd and pooled, when possible, using the method of Mantel and Haenszel (13, 27). Homogeneity of response to treatment among herds was assessed using the Breslow-Day chi-square test. Days to first observed estrus, first service, and pregnancy were assessed using survival analysis. Data were initially examined using the univariate log-rank method (5) and were further evaluated using Cox proportional hazards regression (5) with adjustments for the effect of herd. Crude and adjusted hazard ratios (HR) derived using survival techniques reflected the risk of each outcome in treated versus control cows. The significance of HR obtained from log-rank and Cox's proportional hazards model was assessed using the Mantel Cox or likelihood ratio chi-squares, respectively. Proportional hazards assumptions used in survival models were tested by examining log minus log plots and fitting time-dependent covariates.

The milk fat and protein percentages that were recorded for each herd test were summed and then multiplied by milk production for that test to produce a combined variable representing total fat and protein yields or total solids. Milk production, total solids, mean milk production, and mean solids obtained from the first 4 herd tests were examined as possible predictor variables for reproductive efficiency. The crude odds ratio (OR) for pregnancy was defined as the ratio of the odds of treatment for pregnant cows versus nonpregnant cows. Logistic regression (5) was used to determine the effect of the lactation variables defined previously on the odds for pregnancy with and without adjustment for the effect of treatment. Survival analysis (5) was used to test the effect of each variable on the hazard for pregnancy with and without adjustment for state and herd. Data for both lactation and reproductive events were available for 908 cows.

Disease data. Fifteen categories of disease were examined. Health data were recorded by farm personnel as a part of routine herd health services conducted by the managing veterinarians on each participating farm. All herds recorded the incidence of metritis and retained fetal membranes (RFM). The remaining disease outcomes were recorded for all herds in QLD and NSW, a total of 686 cows. The incidence rate of each disease was defined as the number of new cases reported within treatment or control groups during the study period divided by the total number of cows within that group. The RR were pooled, and homogeneity was assessed, using the same methods as detailed for reproductive data. In many cases, the incidence of a disease within individual states or herds was 0 or too low to provide meaningful comparisons when the groups were pooled. The risks of mastitis and lameness were examined using survival analysis as described previously.

Lactation data. Monthly herd test data were obtained from herd recording services. Herd test milk volume (liters), fat percentage, fat yield (kilograms), protein percentage, and protein yield (kilograms) were analyzed. Following initial evaluation, a multi-level, repeated measures mixed model was used in which herd was included as a random effect. The model was used to compare the two groups over 10 herd tests for milk production, fat yield, fat percentage, protein yield, and protein percentage (34). The repeated measures model provided tests for the following three hypotheses: 1) there was no significant difference between the adjusted means of treatment and control groups, 2) the variable concerned did not vary with time, and 3) the pattern of change in the
variable over successive measurements was equivalent for treatment and control groups. Cows (n = 915) that contributed to at least 6 monthly herd tests were included in analyses of milk production and fat and protein yields. If cows did not subsequently contribute to any of the remaining 4 herd tests, these variables were recorded as 0. When a herd test was missed and the cow had not been removed from the milking herd, previous and proceeding values were averaged. Cows that produced milk for at least 6 herd tests were also included in the analyses of fat and protein percentages. If cows did not subsequently contribute to any of the remaining 4 herd tests, these variables were recorded and analysed as missing data.

RESULTS

Effects of Monensin on Reproductive Performance

The crude RR, which is the ratio of pregnancy responses of treated cows to the proportion of pregnancy responses of control cows, was 1.01, and was not significantly different between groups (95% CI, 0.95 to 1.06) (Table 1). With a conception rate of 0.83 for controls and \( \alpha = 0.05 \), the power (1 - \( \beta \)) to detect a significant difference of 10% between treatment groups was 0.99. The effect of monensin varied among herds (\( P = 0.02 \)); however, a sensitivity analysis indicated that the variation of the effect of monensin could be attributed to one of the herds from NSW (Table 2). The results, apart from the findings in this one herd, were homogenous.

Treatment with monensin did not influence the crude risk of pregnancy at first service (RR = 0.94; 95% CI, 0.84 to 1.04) (Table 1). With a conception rate at first service of 0.59 in controls and \( \alpha = 0.05 \), the power (1 - \( \beta \)) to detect a significant difference of 10% between the treatment and control groups was 0.90. The effect of monensin on the RR of pregnancy at first service differed among herds (\( P = 0.007 \)) (Table 1).

Figures 1, 2, and 3 show, respectively, the survival curves for days to first observed estrus, days to first service, and days to conception for treated and control cows. The crude HR for first observed estrus, first service, and pregnancy were 1.04 (\( P = 0.54 \)), 1.00 (\( P = 0.98 \)), and 0.96 (\( P = 0.50 \)), respectively (Table 3). The HR is the ratio of the proportion of cows surviving in the treatment group over the proportion of cows surviving in the control group each day. Adjustment for the effect of herd did not substantially alter either the magnitude or significance of these HR (Table 3).

After adjustment for the effect of treatment, milk production obtained from herd test 1 reduced the hazard of pregnancy by 1%/L of milk (\( P = 0.012 \)).
TABLE 2. Relative risks (RR), 95% confidence intervals, and Mantel-Haenszel (MH) combined RR for pregnancy and pregnancy at first service for cows treated with monensin and control cows.

<table>
<thead>
<tr>
<th>Outcome and farm1,2</th>
<th>Treated cows</th>
<th>Control cows</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(no./total no.)</td>
<td>(no./total no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43/46</td>
<td>40/43</td>
<td>1.00</td>
<td>0.90–1.12</td>
</tr>
<tr>
<td>2</td>
<td>73/85</td>
<td>62/79</td>
<td>1.09</td>
<td>0.95–1.26</td>
</tr>
<tr>
<td>3</td>
<td>52/58</td>
<td>52/67</td>
<td>1.16</td>
<td>0.99–1.35</td>
</tr>
<tr>
<td>4</td>
<td>18/20</td>
<td>12/16</td>
<td>1.20</td>
<td>0.87–1.65</td>
</tr>
<tr>
<td>5</td>
<td>15/19</td>
<td>14/19</td>
<td>1.07</td>
<td>0.75–1.53</td>
</tr>
<tr>
<td>6</td>
<td>22/37</td>
<td>27/44</td>
<td>0.97</td>
<td>0.68–1.38</td>
</tr>
<tr>
<td>7</td>
<td>6/15</td>
<td>16/18</td>
<td>0.45</td>
<td>0.24–0.85</td>
</tr>
<tr>
<td>8</td>
<td>14/18</td>
<td>12/18</td>
<td>1.17</td>
<td>0.77–1.76</td>
</tr>
<tr>
<td>9</td>
<td>22/26</td>
<td>18/19</td>
<td>0.89</td>
<td>0.73–1.09</td>
</tr>
<tr>
<td>10</td>
<td>24/27</td>
<td>13/16</td>
<td>1.09</td>
<td>0.83–1.43</td>
</tr>
<tr>
<td>11</td>
<td>81/87</td>
<td>93/94</td>
<td>0.94</td>
<td>0.89–1.00</td>
</tr>
<tr>
<td>12</td>
<td>74/92</td>
<td>79/93</td>
<td>0.95</td>
<td>0.83–1.00</td>
</tr>
<tr>
<td>Pregnancy at first service4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22/43</td>
<td>21/40</td>
<td>0.97</td>
<td>0.64–1.48</td>
</tr>
<tr>
<td>2</td>
<td>41/80</td>
<td>31/76</td>
<td>1.26</td>
<td>0.89–1.77</td>
</tr>
<tr>
<td>3</td>
<td>32/54</td>
<td>25/55</td>
<td>1.30</td>
<td>0.91–1.88</td>
</tr>
<tr>
<td>4</td>
<td>11/20</td>
<td>8/16</td>
<td>1.10</td>
<td>0.59–2.07</td>
</tr>
<tr>
<td>5</td>
<td>8/19</td>
<td>9/19</td>
<td>0.89</td>
<td>0.44–1.81</td>
</tr>
<tr>
<td>6</td>
<td>14/25</td>
<td>19/30</td>
<td>0.96</td>
<td>0.63–1.47</td>
</tr>
<tr>
<td>7</td>
<td>3/13</td>
<td>9/17</td>
<td>0.44</td>
<td>0.15–1.30</td>
</tr>
<tr>
<td>8</td>
<td>8/16</td>
<td>10/15</td>
<td>0.75</td>
<td>0.41–1.38</td>
</tr>
<tr>
<td>9</td>
<td>15/24</td>
<td>13/19</td>
<td>0.91</td>
<td>0.59–1.41</td>
</tr>
<tr>
<td>10</td>
<td>14/25</td>
<td>11/13</td>
<td>0.66</td>
<td>0.44–1.00</td>
</tr>
<tr>
<td>11</td>
<td>52/87</td>
<td>70/94</td>
<td>0.80</td>
<td>0.65–1.09</td>
</tr>
<tr>
<td>12</td>
<td>51/91</td>
<td>57/92</td>
<td>0.90</td>
<td>0.71–1.15</td>
</tr>
</tbody>
</table>

1Herds 1 through 3 were selected from the Atherton Tablelands (Queensland, Australia), herds 4 through 10 were selected from the Camden district (New South Wales, Australia), and herds 11 and 12 were selected from the Golburn Valley (Victoria, Australia).

2Data are stratified by farm.

3Heterogenous strata (P = 0.02); combined RR (MH) were not calculated.

4Heterogenous strata (P = 0.007); combined RR (MH) were not calculated.

However, results were not significant (P = 0.23) after adjustment for the effect of herd. The effect of treatment on the hazard of pregnancy was not significant when adjusted for milk production at herd test 1 (P = 0.32) or when further adjusted for herd (P = 0.28). No interaction (P = 0.60) between the effects of treatment and milk production on the hazard of pregnancy was observed. Milk production and fat and protein yields at the remaining herd tests did not alter the hazard of pregnancy (P > 0.14). Adjustment for the effects of herd did not change these results.

The crude OR for pregnancy in treated versus control cows was 0.71 (P = 0.12). This OR was not substantially altered by adjustment for any lactation variable. When examined independently, increasing milk production and total solids and mean milk production and total solids tended (P > 0.38) to increase the odds for pregnancy. Adjustment for treatment did not alter these results.

**Effects of Monensin on Health**

Treatment with monensin did not reduce (P > 0.08) the risk of dystocia, ketosis, milk fever, infectious disease, metritis, RFM, lameness, or abortion nor increase the risk of mastitis (Table 4). The crude RR of pyometra was 1.00. Hypomagnesemia, gastrointestinal dysfunction, clinical parasitic disease, down cow syndrome, teat injury, and miscellaneous udder disorders were not reported for either group, and, for

TABLE 3. Crude and adjusted hazard ratios (HR) and P values for first observed estrus, first service, and pregnancy (days open).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude HR</th>
<th>P</th>
<th>Adjusted HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to first observed estrus</td>
<td>1.04</td>
<td>0.37</td>
<td>1.04</td>
<td>0.61</td>
</tr>
<tr>
<td>Days to first service</td>
<td>1.00</td>
<td>0.98</td>
<td>1.04</td>
<td>0.51</td>
</tr>
<tr>
<td>Days to conception</td>
<td>0.96</td>
<td>0.46</td>
<td>0.95</td>
<td>0.50</td>
</tr>
</tbody>
</table>
TABLE 4. Crude relative risks (RR) and 95% confidence intervals for each disease for cows treated with monensin and control cows.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treated cows (no./total no.)</th>
<th>Control cows (no./total no.)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystocia</td>
<td>14/350</td>
<td>15/336</td>
<td>0.90</td>
<td>0.44–1.83</td>
</tr>
<tr>
<td>Ketosis</td>
<td>1/350</td>
<td>1/336</td>
<td>0.96</td>
<td>0.06–15.29</td>
</tr>
<tr>
<td>Milk fever</td>
<td>4/350</td>
<td>6/336</td>
<td>0.64</td>
<td>0.18–2.25</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>2/350</td>
<td>2/336</td>
<td>0.96</td>
<td>0.14–6.78</td>
</tr>
<tr>
<td>Gastrointestinal dysfunction</td>
<td>0/350</td>
<td>1/336</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Down cow</td>
<td>0/350</td>
<td>0/336</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Metritis</td>
<td>22/543</td>
<td>23/525</td>
<td>0.92</td>
<td>0.52–1.63</td>
</tr>
<tr>
<td>Pyometra</td>
<td>1/350</td>
<td>1/336</td>
<td>0.96</td>
<td>0.06–15.29</td>
</tr>
<tr>
<td>RFM</td>
<td>28/543</td>
<td>37/525</td>
<td>0.73</td>
<td>0.45–1.17</td>
</tr>
<tr>
<td>Mastitis</td>
<td>39/350</td>
<td>35/336</td>
<td>1.07</td>
<td>0.70–1.65</td>
</tr>
<tr>
<td>Teat injury</td>
<td>0/350</td>
<td>2/336</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Lameness</td>
<td>15/350</td>
<td>25/336</td>
<td>0.58</td>
<td>0.31–1.08</td>
</tr>
<tr>
<td>Accidents</td>
<td>0/350</td>
<td>1/336</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Abortion</td>
<td>2/350</td>
<td>7/336</td>
<td>0.27</td>
<td>0.06–1.31</td>
</tr>
</tbody>
</table>

1Not calculated.
2Retained fetal membranes.

These outcomes, crude RR were not calculated. The crude HR for mastitis and lameness in treated versus control cows were 1.09 (P = 0.70) and 0.55 (P = 0.07), respectively. Adjustment for herd did not substantially alter either the significance or magnitude of the HR (Table 5).

Effect of Monensin on Milk Production and Milk Constituents

Mean milk production was increased by treatment (Figure 4) after adjustment for herd (P = 0.0001).

Figure 3. Survival curves for pregnancy (days open) (n = 905) for cows treated with monensin (--), control cows (---), cows with complete records (○), and cows that were censored (+).

Figure 4. Mean adjusted milk production (n = 915) for cows treated with monensin (○) and control cows (■).

This effect was consistent throughout lactation (P = 0.52) but differed among herds (P = 0.02). The power (1 - β) to detect a significant difference of 10% in milk production between treatment groups was 0.85; the pattern of change in milk production with successive herd tests was 1.00.

Milk fat yield was not increased by monensin treatment (Figure 5) after adjustment for herd (P = 0.2). Similarly, monensin treatment did not alter the pattern of change in fat yield throughout lactation after adjustment for herd (P = 0.43). Treatment did not increase milk protein yield (Figure 6) after adjustment for herd (P = 0.49). The effect of treatment was consistent throughout lactation (P = 0.67). Fat percentage in milk was not reduced by monensin treatment (P = 0.15) (Figure 7), and treatment did not alter the pattern of change in fat percentage during lactation (P = 0.32) (Figure 6). Monensin did not increase milk protein percentage (P = 0.11) (Figure 8), and the pattern of change in protein percentage...
Figure 5. Mean adjusted milk fat yield (n = 915) for cows treated with monensin (◇) and control cows (●). During lactation did not differ (P = 0.99) between treated and control cows.

**DISCUSSION**

This multiple-center, randomized controlled trial was designed primarily to examine the effects of monensin on the fertility of dairy cows. Secondary objectives were to examine the effects of monensin on health and milk production and composition. A multiple-center trial design was used to improve generalizability and external validity. Strengths of the trial included a high statistical power to examine the effects of treatment on reproduction and milk production and composition. The trial utilized herds that were selected on the basis of high quality records. These herds may, therefore, have differed in some other aspects of management compared with the population from which they were drawn.

**Effects of Monensin on Reproductive Performance**

Higher energy balance and plasma glucose concentrations and lower plasma ketone concentrations may be important determinants of postpartum reproductive performance of dairy cows (7, 37). Monensin treatment can increase glucose flux (18), reduce serum ketone concentrations (1, 35, 40), modify pituitary and ovarian function (32, 33), and shorten the interval from calving to the return to first observed estrus in dairy cows (1). In this study, however, monensin treatment did not alter the PR or first service PR (Table 2), although the effect of monensin treatment on pregnancy differed among herds (P < 0.03). Much of the variation in pregnancy among herds could be attributed to the significant negative result in a small number of treated cows in 1 herd from NSW. When significant heterogeneity or effect modification exists, the statistical assumptions used to combine stratum-specific rates do not hold, and the crude estimates for the RR of each outcome are preferred (17). The effect of monensin on pregnancy was apparently modified by managerial, environmental, or nutritional differences that existed among herds.

After adjustment for the effects of herd, treatment with monensin did not significantly increase the hazard for first observed estrus and first service nor did it decrease the hazard for pregnancy. These effects (Table 2) were consistent with those of similar trials in Australia (23) and New Zealand (21) in which cows were treated with a single bolus immediately after calving or before the commencement of breeding. Abe et al. (1), however, reported a significantly decreased hazard for first observed estrus in cows treated with monensin but found no significant evidence for a difference in the number of days to first ovulation. Cows from a subpopulation of our trial had lower ketone concentrations before and after calving...
Figure 7. Mean adjusted milk fat percentage (n = 915) for cows treated with monensin (◊) and control cows (●).

(40), and treated cows in similar studies (1, 18) had higher glucose concentrations. If these changes in metabolites were present in all treated cows, the role of increased plasma glucose concentrations and lower ketone concentrations on reproductive function of cows would need to be investigated.

Many studies (22, 24, 30) have identified associations between higher milk production and lower reproductive performance. We hypothesized that if the production of milk or milk solids was a major determinant of reproductive efficiency, then impairment of reproductive performance or efficiency might occur in proportion to their production. None of the lactation variables examined influenced the PR with or without adjustment for the effect of treatment. Although milk production at herd test 1 reduced the hazard for pregnancy by 1%/L of milk (P = 0.012), adjustment for herd effects indicated no significant effect of either milk production or treatment on the hazard of pregnancy. Although monensin may influence fertility in cows in some herds, the findings of this and similar studies (21, 23) showed no significant effect of monensin treatment on fertility, and milk production did not modify this effect.

**Effects of Monensin on Health**

Although cows treated with monensin had a lower incidence of ketosis, RFM, metritis, pyometra, dystocia, lameness, abortion, and infectious disease and a higher incidence rate of mastitis, there were relatively few cases of any of these diseases, and the power to identify a significant treatment effect was low. Therefore, for example, although 37% of the reduction in the rate of RFM in cows treated with monensin could be attributed to treatment (P = 0.20), more studies are required to determine whether nonsignificant reductions in risk of RFM or other health conditions resulted from treatment or chance. Monensin increases selenium and copper absorption (8) and may, therefore, influence the risk of RFM. Caeruloplasmin concentrations in a subpopulation of cows treated with monensin from this trial were significantly increased, although the concentration of GSHPx was not altered (40).

Seventy-two percent of the reduced rate of lameness observed in treated cows could be attributed to treatment with monensin (P = 0.08). Subclinical aseptic laminitis has a nutritional aetiology. A decrease in the risk of ruminal acidosis decreases the risks of acute, chronic, and subclinical aseptic laminitis (45). Cows treated with monensin maintained a higher ruminal pH when challenged with experimentally induced lactic acidosis (29). Treatment has also increased production of propionate, decreased production of butyrate and lactate (6, 10), and maintained the metabolism of lactate to propionate (16). Monensin inhibits the growth of Streptococcus bovis and Lactobacillus spp. (9). Therefore, it is possible that monensin treatment decreased the lameness associated with subclinical acidosis in this study.

Figure 8. Mean adjusted milk protein percentage (n = 915) for cows treated with monensin (◊) and control cows (●).
Monensin modifies the flux of ions across intestinal epithelial cells (36) and increases uptake and availability of dietary minerals, including calcium (13, 40). Therefore, we postulated that treatment may alter the risk of milk fever. Monensin did not significantly lower the incidence of milk fever, and Stephenson et al. (40), using a subpopulation of 24 cows from this study, were unable to identify an increase in plasma calcium concentrations in treated cows.

Stephenson et al. (41) found that neutrophils obtained from a subpopulation of cows treated with monensin from this study had greater chemotaxis than did those obtained from controls. Monensin tended to reduce the rate of metritis, pyometra, and infectious disease, although the differences were not significant. The lower incidence rate of abortion for cows treated with monensin suggests that monensin may influence the risk of abortion. Monensin could possibly exert an antiprotozoal action against Neospora caninum, a common cause of abortion in cows. No significant increase in the risk of mastitis was observed (Table 4) despite the significantly higher milk production observed for treated cows. Increased risk of mastitis has been observed when milk production was increased because of breeding for increased genetic merit (47) and when cows were treated with exogenous somatotropin (25, 46).

Incidence rates for diseases of Australian dairy cows have not commonly been reported. For control cows, incidence rates of each disease were, therefore, compared with those for other countries with similar dairy industries. The incidence rates of dystocia (4%), RFM (7%), teat injury (1%), lameness (7%), and abortion (2%) were similar to those reported by Dohoo et al. (11). That Canadian study (11) used herds fed rations based on hay, corn, and silage; the herds were permanently housed in tie-stall barns and were intensively monitored for abnormalities of health by visiting veterinarians. The incidence rates of dystocia, RFM, teat injury, and abortion were also similar to those reported by Gröhn et al. (19) in a Finnish study using 61,124 Ayrshire cows. Incidence of lameness varied substantially among herds, although the range was similar to the range reported by Tranter and Morris (42), who suggested a mean incidence rate of 21% and a range of 6% in three New Zealand dairy herds. Dewes (10) reported an incidence rate of 14% for dairy herds in New Zealand, and Gröhn et al. (19) reported an incidence rate for lameness of 1.9% for Finnish dairy cows.

The incidence rates of ketosis (0.30%), milk fever (2%), gastrointestinal dysfunction (0.30%), down cow syndrome (0.30%), metritis (4.40%), pyometra (0.30%), and mastitis (10%) observed in our study were lower than the incidence rates reported by Dohoo et al. (11). With the exception of ketosis, however, which was lower in our study, these rates were similar to those reported by Gröhn et al. (19). In an analysis of the full lactations of 914 European and American cows, White et al. (46) reported an incidence rate in the control group that was very similar to that observed in our study. In our study, most diseases had low incidence rates, which may reflect a lower frequency of disease in Australian dairy herds than in herds that are more intensively housed and fed, although the use of selected herds and the possibility of underrecording by the farmers were factors that could have reduced the apparent incidence of disease.

Effects of Monensin on the Production of Milk and Milk Constituents

Treatment of lactating dairy cows with monensin has increased milk production (21, 23, 26, 43). We found that treatment with monensin significantly increased milk production by a mean of 0.75 L/d per cow after adjustment for the effect of herd. Diets that increase propionate flux and decrease the mobilization of FFA tend to suppress milk fat yield (2). Monensin increases the production of propionate and may decrease the mobilization of FFA (1, 40). Treatment with monensin has not generally altered milk fat yield (23, 26), although milk fat percentage may be reduced (1, 26, 43). We found that, after adjustment for the effect of herd, monensin increased milk fat yield (P > 0.06) but did not decrease milk fat percentage (P > 0.42) during either early or late lactation.

Treatment with monensin has decreased ruminal degradation of dietary protein (20), increased nitrogen retention (20, 36), increased propionate flux, and increased the availability of lysine and methionine and other amino acids to the small intestine (20). Therefore, we proposed that monensin might increase milk protein yield. We found that, after adjustment for the effect of herd, monensin did not significantly alter the yield or percentage of milk protein, although both varied significantly among herds. These results were similar to those of Sauer et al. (35) and Abe et al. (1), although Lowe et al. (26) found that monensin increased protein yield, and Lean et al. (23) reported that treatment increased protein yield in some herds.

Treatment with monensin 40 d prior to and 50 d following calving did not significantly alter the pat-
tern of change in milk production, fat yield, fat percentage, protein yield, or protein percentage with successive herd tests. These results are in contrast to those of Lean et al. (23) who administered a single bolus at the time of calving and observed differences in the curves for milk production and protein yield of treated and control cows, which, in some herds, approached significance. This disparity suggested that the administration of monensin before and after calving was necessary to obtain treatment effects that are sustained throughout lactation.

CONCLUSIONS

This large multiple-center trial found that monensin treatment before and after calving increased milk production, did not significantly influence fertility measures, but might alter the risk of some diseases of dairy cows. Some variability was apparent in pregnancy responses to treatment among herds. The response to treatment has been variable in previous studies, which suggests a need for further definition of the environment and feeding practices in future studies. It may be possible to use the techniques of meta-analysis to combine the results of this study with those from similar large trials and to provide greater power to investigate the possible impact of monensin on reproduction and milk production.

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