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Effect of anthelmintics on reproductive performance and first-lactation culling rate in Holstein heifers

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Female Holstein calves were treated with ivermectin from birth to first oestrus to study the effect of parasitic burden and anthelmintic treatment on reproductive and productive performance. First oestrus, age at first service and age at calving were advanced by 30, 70 and 110 days, respectively (P<0·05), in ivermectin-treated animals compared with controls. No significant differences were observed in the conception rate, the number of services and the characteristics of the newborn calves and any problems at calving between the two groups. Daily milk yield, fat content in milk during first lactation, and the concentrations of growth hormone, insulin-like growth factor type 1, insulin and prolactin in serum were similar in both groups of cows. Culling during the first lactation was more common in untreated (47 per cent) than in treated (11 per cent) cows (P<0·05).

ON Argentinian farms, replacement dairy heifers are commonly reared outdoors from birth, and ingest nematode larvae with forage, resulting in different degrees of infection. Larvae are mostly *Ostertagia* and *Cooperia* species, but *Haemonchus*, *Trichostrongylus* and *Nematodirus* species are also seen (Mejía and others 1999). Heifers are exposed to the highest numbers of larvae in early summer and early winter (Suarez 1990).

In beef herds it has been shown that helminth parasites decrease average daily gain (ADG) of bodyweight and delay sexual maturation (Ambrustolo and others 1990, Zajac and others 1991), and anthelmintic treatment of beef and dairy heifers has been associated with early onset of first oestrus (Larson and others 1995, Purvis and Whittier 1996, Mejía and others 1999). The effect on the endocrine system, which has been suggested to influence these changes, has been studied, and an increase of insulin-like growth factor type 1 (IGF-1) serum levels, with no increase in serum growth hormone (GH), was seen in dairy heifers treated with ivermectin before first oestrus (Lacau-Mengido and others 2000, Díaz-Torga and others 2001). In addition, ivermectin-treated heifers had a larger pelvic size, suggesting that ivermectin treatment before first oestrus might improve outcomes at parturition (Mejía and others 1999).

Age at first oestrus indirectly influences production efficiency in dairy cows, and IGF-1 levels may affect this parameter directly by its involvement in mammary gland development. It has been suggested that GH plays an important role in mammary ductal morphogenesis during puberty, and that its action is mediated by IGF-1 (Kleinberg 1998).

The aim of this study was to determine the effect of a parasitic burden and anthelmintic treatment up to first oestrus on the reproductive and productive performance of heifers. Untreated control heifers were compared with heifers treated with ivermectin from birth to first oestrus. Pregnancy, age at calving, and cases of abortion were monitored. Milk production, and circulating hormones involved in reproduction and milk production, were also evaluated during the first lactation.

Materials and methods

Twenty heifers were treated with 0·2 mg/kg ivermectin (Ivomec; MSD AgVet), given subcutaneously, every 14 days from birth to first oestrus as previously described by Díaz-Torga and others (2001). Twenty age-matched untreated heifers were used as controls. Faeces were collected for nematode egg counting every two weeks throughout the treatment period. Onset of oestrus was assessed by measuring serum progesterone weekly, and serum IGF-1 levels were also measured throughout this period. The heifers were managed outdoors from the day of birth, both groups grazing together, at the dairy farm at the experimental school of Inchausti, Argentina (35°36′ S, 60°32′ W). For the first two months they were kept in individual pens on the pastures and moved as the pasture was exhausted. They were fed two litres of warm milk twice a day and had ad libitum access to a balanced supplement. After two months they were mixed into the grazing herd and grazed on alfalfa and/or ryegrass pastures, in a rotational grazing system (stocking density eight animals/ha), with ad libitum access to the supplement. Once the animals reached 160 kg bodyweight, the supplement was changed to corn (2 kg/animal/day) and the stocking density was reduced to two animals/ha. Once they reached 350 kg, they were moved to the insemination herd and monitored twice daily for standing heat, the standard sign for oestrus, by a trained observer. They were inseminated artificially. All the heifers received semen from the same sire to avoid differences in male fertility. If oestrous signs did not reappear in 40 days, pregnancy was determined by rectal palpation. If oestrus occurred again a repeat artificial insemination was performed. If the animal did not become pregnant the protocol was repeated up to four times. If oestrus occurred a fifth time the heifer was culled.

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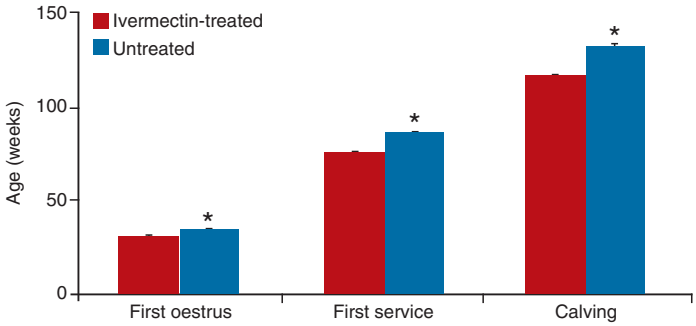

FIG 1: Age at first oestrus, first service and calving in ivermectin-treated and untreated heifers. *P<0·05

TABLE 1: Features of calving (mean [se]) groups of heifers (n=18) treated with ivermectin from birth to first oestrus, or left untreated

	Untreated	Ivermectin-treated
Bodyweight (kg)	413 (5)	401 (6)
Withers height (cm)	1376 (9)	1376 (10)
Parturition disorders	4/17*	4/18
Weight of newborn calves (kg)	43·2 (0·9)	41·2 (3·1)
Stillborn calves	2/17*	2/18
Sex of calves	9 male, 8 female	10 male, 8 female

* One heifer aborted and was removed from the group

At day 160 of pregnancy, the heifers were moved to the dairy dry herd. Two days before the expected calving date the heifers were weighed and their withers height was measured (Weaver 1987). Newborn calves were weighed and their sex was recorded. Parturition disorders, such as dystocia and retained fetal membranes, were recorded. Twenty-four hours after parturition the cows were moved to the milking herd. The cows grazed outdoors on ryegrass, alfalfa and/or clover pastures (mean stocking density 1·5 animals/ha) and received a supplement of a total mixed ration containing corn grain, sunflower and/or cotton seeds, calcium chloride and corn silage in accordance with nutritional requirements and individual milk production. They were milked twice a day. Individual daily milk production was recorded by means of the Alpro milking system (DeLaval) and a blood sample was obtained by venepuncture of the coccygeal vein once a month during the whole lactation period for insulin, IGF-1, GH and prolactin measurements.

Normal uterine involution between 20 and 40 days postpartum was assessed by palpation per rectum. After 45 days the cows were inseminated once oestrus was detected. If oestrous signs reappeared, artificial insemination was repeated. Sixty days before the probable parturition date or when milk production declined below 12 litres/day, the cows were dried off.

Health, reproductive and productive records were recorded using the Syscord-Tamb (Lincoln) program. All experimental procedures involving the use of animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Instituto de Biología y Medicina Experimental, Buenos Aires (Division of Animal Welfare).

Hormone determinations

Progesterone was determined by radioimmunoassay (RIA), performed as previously described by Mejía and others (1999). Assay sensitivity was 50 pg/tube, and intra-assay and interassay coefficients of variation were 7·5 per cent and 11·9 per cent, respectively. Antibody was provided by G. D. Niswender and labelled progesterone was purchased from Dupont NEN. When levels of progesterone exceeded the 1·0 ng/ml the heifers were considered to be pubertal. GH and prolactin were measured by RIA as previously described (Lacau-Mengido and others 2000, Díaz-Torga and others 2001), using anti-ovine antibodies (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]). Intra-assay coefficients of variation were less than 7·5 per cent. Minimum detectable concentrations were 0·8 ng for both hormones. The IGF-1 RIA was performed after acid-ethanol extraction as previously described by Lacau-Mengido and others (2000). The IGF-1 antibody (UB2-495) (Hormone Distribution Program, NIDDK) was used. The intra-assay coefficient of variation was 7·2 per cent. The minimum detectable concentration was 2·5 ng. Insulin was measured by RIA as described by Díaz-Torga and others (2001), using anti-bovine insulin antibody (Sigma), and standard human insulin (Laboratorios Beta). The intra-assay coefficient of variation was 7 per cent. The minimum detectable concentrations were 2 ng.

Statistical analysis

Age and bodyweight at first oestrus, first service and calving were analysed using analysis of variance (ANOVA). Milk production, milk fat content and hormone values were analysed using two-way ANOVA for repeated measurements, for the effects of days in milk and treatment.

Conception to first service and culling rates were compared between treatments by chi-squared tests. The number of services per pregnancy was compared between groups with Fisher's exact test, and the interval from calving to conception with *t* tests for independent samples.

Results

Faeces of ivermectin-treated heifers remained free from parasite eggs until the end of the treatment period, whereas untreated heifers had nematode infections with a course similar to those previously described in detail by Mejía and others (1999), with a rapid increase in epg at 12 weeks of age until weeks 18 to 20, when the faecal egg count peaked at approximately 1000 epg, and then decreased to 200 epg by week 28. At the end of the treatment period, egg counts were approximately 100 epg. Ivermectin-treated heifers reached first oestrus before untreated animals (mean [sd] 211 [6] v 242 [10] days of age) (P<0·05) at the same bodyweight (183 [4] and 178 [5] kg, respectively).

The measured concentrations of IGF-1 in blood were higher in treated than in untreated heifers from five months of age onward, as previously described by Lacau-Mengido and others (2000). At first oestrus, IGF-1 levels were 18·9 (2·7) ng/ml for ivermectin-treated heifers and 10·9 (1·3) ng/ml for untreated heifers (P<0·05). Two heifers from the treated group and one from the untreated group were removed from the study because of morphological abnormalities of the udder and hindlimbs. One further heifer from the untreated group died before first oestrus for unknown reasons. Treated heifers entered the insemination herd on average 48 days before the untreated ones (ivermectin-treated 468 [7], untreated 516 [8] days of age) (P<0·05). The first service was performed 70 days earlier in the treated heifers (523 [10] days of age) compared with the untreated heifers (594 [11] days of age) (P<0·05) (Fig 1).

The percentage of heifers that conceived to first service (treated 68·8 per cent, untreated 57·9 per cent) (P=0·31) and the number of services per pregnancy (treated 1·56, untreated 2·21) (P=0·83) were not significantly different between the groups. However, only three of the 18 treated heifers required more than one service, compared with six of the 18 untreated heifers. In addition, one animal from the untreated group aborted and was removed from the group.

Heifers treated with ivermectin were younger than untreated heifers at parturition (Fig 1). The bodyweight and withers height at calving were similar in both groups. The bodyweight and sex of the calves, incidence of dystocia and number of stillborn calves were not significantly different between the groups (Table 1).

Daily milk yield and milk fat content were not significantly different between the groups during first lactation (Fig 2). Furthermore, when the cows were bred, no differences were found in the interval from parturition to first service, the first service conception rate and the number of services per pregnancy (data not shown). Culling rates during first lactation were significantly different between the groups (treated 11·1 per cent, untreated 47·0 per cent) (P<0·05).

Endocrine patterns during lactation are shown in Fig 3. GH peaked at 60 days in milk and then decreased gradually until the end of lactation. IGF-1 and insulin were stable throughout lactation. Prolactin had an irregular profile, but its levels tended to decrease between the beginning and the end of lactation. Hormone levels did not differ significantly between groups during the first lactation.

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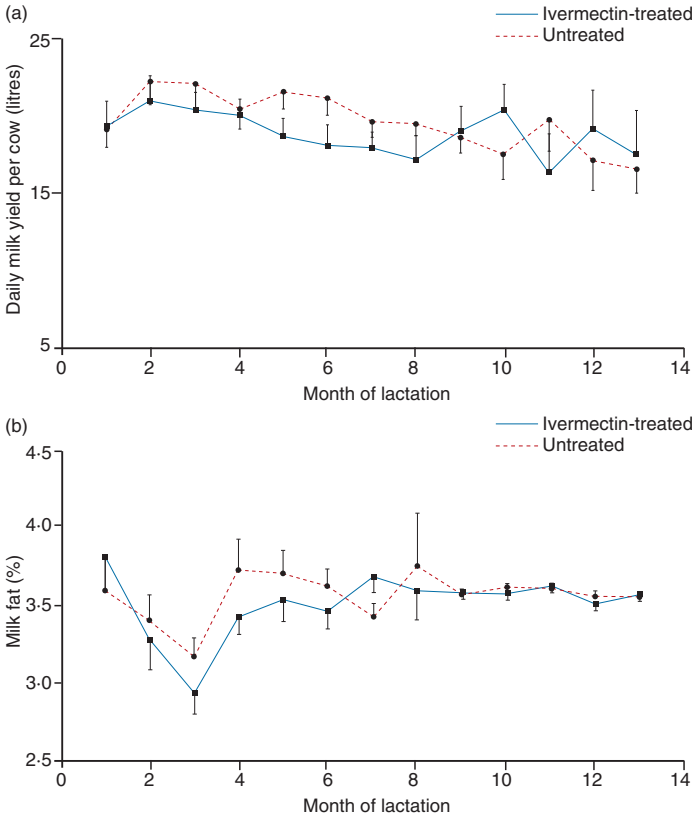

FIG 2: (a) Daily milk production and (b) milk fat content during first lactation of cows that had been treated with ivermectin, or left untreated, during development

Discussion

Frequent ivermectin treatment of the heifers in this study during their development decreased the age of first oestrus compared with controls (Mejía and others 1999). Untreated heifers had a significant delay in reaching the bodyweight for breeding, age at first service, and age at parturition. These events occurred at a similar bodyweight for both groups. This suggests that, despite the cessation of ivermectin treatment at first oestrus, the effect on body growth is observed postpubertally, and bodyweight does not even out until adulthood. Furthermore, the one-month difference to first oestrus increased to more than three months for the onset of the first lactation period, which is potentially detrimental to the production potential for untreated heifers.

The slower growing rate of untreated heifers has been reported to be due to lower levels of IGF-1 up to first oestrus (Lacau-Mengido and others 2000); this was supported by the present trial. As the IGF-1 system links somatic development to gonadotropin regulation at first oestrus (Hiney and others 1996), this peptide may also be responsible for delay of puberty. Other metabolic hormones, such as leptin and insulin, may also be involved (Díaz-Torga and others 2001).

Although not significant, the number of heifers that required more than one service to become pregnant was doubled (6 v 3) in the untreated group compared with the treated group. This may indicate an impairment of reproductive efficiency caused by parasite burdens. This would be in agreement with observations of reduced luteal activity in cows with negative energy balance, associated with reduced concentrations of serum IGF-1 (Spicer and others 1990). A larger study group might demonstrate whether this is significant, as 20 cows per group, as at the start of the present study, may not be enough to achieve statistical significance. A reduction in the number of inseminations per conception was observed in adult dairy cows treated with eprinomectin in Canada (Sanchez and others 2002) and an improvement of fertility was reported with different regimens of anthelmintic treatment in the Gambia (Zinsstag and others 1997).

After calving, no differences were observed in daily milk production or milk composition of the two groups. If mammary gland development differed between the groups during growth due to different levels of IGF-1, and the cows were differently prepared for milk production, this was not supported by the results of the present study. No alteration in adult endocrine patterns was observed during the first lactation. These patterns are in agreement with previously reported studies (Meikle and others 2004, Becú-Villalobos and others 2007). In contrast, when anthelmintic treatment was given during lactation, differences in milk production were seen (de Rond and others 1990, Nodtvedt and others 2002, Charlier and others 2007), but metabolic and other hormone levels were not reported in those studies. Similarly, anthelmintic treatment during growth did not appear to influence reproductive parameters when heifers became adult lactating cows. In contrast, in a previous study

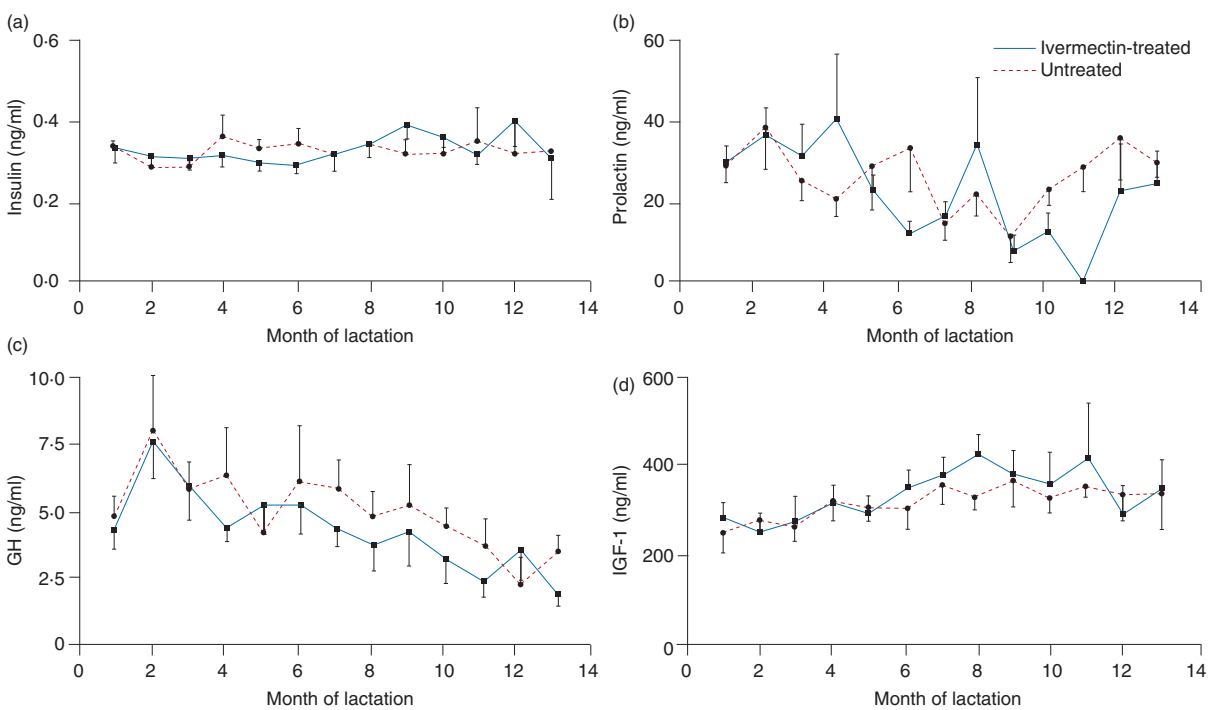

FIG 3: Endocrine patterns during the first lactation of cows that had been treated with ivermectin, or left untreated, during development. (a) Insulin, (b) prolactin, (c) growth hormone (GH), (d) insulin-like growth factor-1 (IGF-1)

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anthelmintic treatment of cows at calving was seen to have a beneficial effect on reproductive parameters (Sanchez and others 2002). However, the results from the present study demonstrate that antiparasitic treatment during development may improve general health in adulthood, as more cows in the treated group, compared with the untreated group, remained in the dairy herd and completed the entire first lactation. The reasons for culling cows from the untreated group were related to hoof and udder health as well as reproductive failure, whereas failure to conceive was the only cause of culling in the treated cows. This may be related to parasite-induced metabolic and nutritional alterations during growth (Coop and Kyriazakis 1999), which in turn affect the immune system and lead to an altered health status (Carroll and Forsberg 2007). However, it has been observed that heifers that were uninfected during the first grazing season had a poorer performance during the second grazing season, and this could be related to the lack of acquired immunity to nematode infection (Ploeger and others 1996). In the present study, immunity to gastrointestinal nematodes once treatment ceased was not evaluated.

The results in the present study were obtained with an intensive schedule of treatment with ivermectin. This was to ensure that the treated group was free of parasites, but is not a management practice to be recommended in commercial herds as it may lead to anthelmintic resistance. The study was designed to show the effect of parasite burden during development in dairy heifers. The effects seen were a decrease in the age of onset of production and so, at a given age, treated animals had produced for a longer period than untreated animals; and an increase in the retention of cows in the lactating herd.

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