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Treatment of pregnancy toxaemia in sheep with flunixin meglumine

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PREGNANCY toxaemia in sheep is a metabolic disorder associated with carrying multiple fetuses (Sargison 2007). It is characterised by hypoglycaemia and hyperketonaemia due to the inability of the ewe to maintain an adequate energy balance in late pregnancy. Common treatments for ewes affected with pregnancy toxaemia include the oral administration of glycerol or propylene glycol solutions, intravenous glucose, and, at more than 135 days of gestation, injection of dexamethasone or betamethasone to induce parturition (Radostits and others 2007), with the aim of eliminating the metabolic demand for energy of the gravid uterus.

Breeding for high prolificacy by the introgression of the Booroola mutation has led to the creation of the highly prolific Afec-Assaf strain of sheep (Gootwine and others 2008). The average prolificacy of Afec-Assaf ewes is 2·55 lambs born per lambing, with approximately 44 per cent of litters containing three or four lambs.

Afec-Assaf ewes are kept in an experimental flock at the Volcani Center, Bet Dagan, Israel, under intensive management conditions, indoors all year round. Reproductive management of the flock includes three to four lambing periods in a year, following oestrus synchronisation, hand-mating and ultrasonographic pregnancy diagnosis at approximately 35 days after mating. The specificity and sensitivity of pregnancy diagnosis for ewes lambing fewer than three lambs (n=388) are 0·93 and 0·89, respectively; in ewes lambing three or more lambs (n=105) the specificity is 0·66 and the sensitivity 0·76 (E. Gootwine, unpublished data). Based on the pregnancy diagnosis results, pregnant ewes are divided into two groups: sheep carrying fewer than three fetuses and sheep carrying three or more fetuses. Both groups are fed to meet their nutritional requirements according to the National Research Council (NRC) recommendations (NRC 1985).

The average prevalence of pregnancy toxaemia in the Volcani Center's Afec-Assaf flock is approximately 0·04, with frequencies of 0·0, 0·01, 0·05, 0·11, 0·25 and 0·33 for lambings with litter sizes of 1, 2, 3, 4, 5 and 6 lambs, respectively (based on 3471 lambings recorded between the years 2000 and 2008). Pregnancy toxaemia is identified at a mean (sd) of 134 (5) days' gestation, and identification is initially based on clinical signs (Sargison 2007). It is later confirmed by monitoring levels of urinary ketone bodies using commercial diagnostic strips (Ketostix; Bayer Diagnostic). Ewes with urinary ketone bodies values of 1·5 mmol/l or more are considered ketotic. The mean (sd) blood β-hydroxybutyrate concentration measured for some of the affected ewes (n=26) was 5·96 (5·09) mmol/l.

TABLE 1: Results of treating ewes affected with pregnancy toxaemia with dextrose and calcium borogluconate alone (2000 to 2004) or in combination with flunixin meglumine (2005 to 2008)

	Dextrose and calcium	Dextrose, calcium and flunixin meglumine
Number of ewes with pregnancy toxaemia	60	83
Number (%) of ewes that died before lambing	12 (20)	4 (5)
Number (%) of ewes that died at or after lambing	35 (58)	6 (7)
Number (%) of ewes that survived	13 (22)	73 (88)
Ewe survival rate	0·22[a]	0·88[b]
Prolificacy (lambs born per ewe lambing)	3·73	3·65
Lambs born alive per ewe lambing	1·87	2·51
Lamb survival rate	0·50[a]	0·69[b]

[a, b] Within rows, different superscript letters denote significantly different values ($P<0·001$)

It has been reported that blood levels of proinflammatory cytokines increase in diabetic patients with ketosis (Hoffman and others 2003, Jain and others 2006). It was therefore hypothesised that hyperketonaemia in pregnancy toxaemia may also be associated with an inflammatory reaction, and that anti-inflammatory treatment may be effective in treating affected ewes. Flunixin meglumine is a potent NSAID (Kopcha and Ahl 1989, Cheng and others 1998a) used to treat respiratory disease, endotoxic shock and mastitis in cattle, and equine colic. It has also been used to treat mastitis in sheep (Fthenakis 2000) and has been applied to reduce pain during mulesing (Paull and others 2007). Based on a preliminary study in which ewes affected with pregnancy toxaemia in commercial flocks were treated successfully with flunixin meglumine (S. Zamir, personal communication), it was decided to add flunixin meglumine to treatments given to Afec-Assaf ewes affected with pregnancy toxaemia at the Volcani Center, from the beginning of 2005.

This short communication describes the treatment of Afec-Assaf ewes affected with pregnancy toxaemia with flunixin meglumine from 2005 to 2008, and compares the results with those obtained between 2000 and 2004 from ewes in the same flock, maintained under the same management conditions, but without flunixin meglumine treatment. Experimental protocols were approved by the Volcani Center's Animal Care Committee.

From 2000 to 2004, all ewes affected with pregnancy toxaemia were treated with 120 ml of 20 per cent (w/v) dextrose solution (Teva Medical) and 50 ml calcium borogluconate (Norbrook) both administered subcutaneously twice a day, from the day that pregnancy toxaemia was diagnosed. The success rate of these treatments was relatively low: 20 per cent of affected ewes died before lambing and 58 per cent of them died at or shortly after lambing (Table 1), similar to the relatively low survival rates obtained in other studies (Buswell and others 1986, Scott and others 1998).

From the beginning of 2005, all pregnancy toxaemia-affected ewes received additional daily intramuscular injections of 50 mg/ml flunixin meglumine (Norbrook) at a dose of 2·5 mg/kg bodyweight, somewhat higher than the dose recommended for cattle by the manufacturer (2·2 mg/kg). Intramuscular rather than intravenous administration was applied, as intravenous administration of NSAIDs in sheep has been found to be lethal in many cases (S. Zamir, personal communication). The duration of flunixin meglumine treatment was based on the responses of the ewes but was never longer than three days.

The immediate effect of the flunixin meglumine treatment was that ewes that had been depressed and reluctant to move got up, walked and

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showed almost normal eating behaviour. Some of the ewes lambed naturally and others lambed after labour induced by dexamethasone treatment. Mean (sd) gestation length in the ewes affected with pregnancy toxaemia was 141 (5) days, which was shorter than the average gestation length of 146 days in Afec-Assaf ewes without pregnancy toxaemia (Gootwine and Rozov 2006).

Lambing results of ewes treated with flunixin meglumine during the period 2005 to 2008 are presented in Table 1. The results show a significant improvement in the survival rate of ewes compared with those obtained during the period from 2000 to 2004 ($P<0{\cdot}001$, chi-squared test), and in the survival rate at birth of lambs born to affected ewes ($P<0{\cdot}001$, chi-squared test). Taking into consideration the fact that the management of the Volcani Center flock was similar during the two periods, the difference in the survival rate of ewes and lambs are suggested to be related to the additional treatment with flunixin meglumine.

Based on the results of this study, it is suggested that flunixin meglumine treatment may provide a means to achieve the full economic potential of high prolificacy: ewe and lamb losses due to pregnancy toxaemia are reduced and the welfare of the animals is improved. Whether the beneficial effect of flunixin meglumine is due to its anti-inflammatory and pain-relieving effects, mediated by an inhibitory effect on prostaglandin formation (Cheng and others 1998b), or occurs through other mechanisms, remains to be investigated. Flunixin meglumine is not yet licensed for use in sheep in the UK; therefore, the possibility that other NSAIDs that are licensed for use in sheep may have a beneficial effect similar to that of flunixin meglumine on pregnancy toxaemia should be addressed.

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