

# Metabolism

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### PRELIMINARY REPORT

## **Inhibition of Fetal Growth and Survival by Testosterone Administration to Pregnant Sheep**

William J. Bremner and I. A. Cumming

Testosterone (as testosterone enanthate, 250 mg i.m. every 2 wk) was administered to pregnant ewes ( $n = 16$ ), and injections of vehicle were used in 10 control pregnant ewes between days 75 of gestation and term (day 147). Fetal survival (7 of 16 in the treated group versus 10 of 10 in the controls) and growth (birth weights  $4.00 \pm 0.51$  kg in the treated group versus  $5.79 \pm 0.93$ , mean  $\pm$  SD, in

the controls) were markedly impaired by testosterone administration. The mechanism of the testosterone effect is unknown, but could be through metabolism to estrogens by the fetoplacental unit. These results imply that alterations in the production or metabolism of androgens by the mother or the fetoplacental unit may exert important effects on fetal growth and survival.

**A** LARGE NUMBER of studies in several species have described effects on fetal and maternal physiology of testosterone (T) administration to pregnant animals.<sup>1</sup> Only rarely, and in sparse detail, have effects of T on fetal growth and survival been mentioned. A recent book on natural and experimental causes of birth weight alterations does not mention an effect of T.<sup>2</sup> The present paper describes pronounced inhibitory effects of T administration to pregnant sheep on fetal growth and survival.

### MATERIALS AND METHODS

Twenty-six Corriedale crossbred ewes, aged 2-4 yr were studied. All were mated in early July (winter) and did not return to estrus. Sixteen ewes (group II) were randomly selected to receive i.m. injections of T enanthate (a long-acting ester), 250 mg in oil at 2 wk intervals. Injections began at approximately day 75 of gestation and were continued until term (approximately day 147

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*From the Medical Research Centre, Prince Henry's Hospital, Melbourne, and Animal Research Institute, Department of Agriculture, Werribee, Victoria, Australia.*

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*Address reprint requests to William J. Bremner, M.D., Division of Endocrinology, U.S. Public Health Service Hospital, Box 3145, Seattle, Wash. 98114.*

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**Table 1. Comparison of the Number of Live Births, Birth Weights, and Gestation Lengths of Lambs Born to Ewes Treated With Testosterone During Pregnancy and to Control Ewes not Treated With Testosterone During Pregnancy**

Group	No of Lambs/ No of Ewes	Weight of Lambs (kg)*	Gestation Length (days)*
I (controls)	10/10	5.79 ± 0.93	146.5 ± 1.69
II (testosterone-treated)	7/16	4.00 ± 0.51	147.5 ± 1.91
Statistical significance between groups	$p < 0.05$	$p < 0.01$	$p > 0.2$

\*Mean ± SD.

of gestation). Ten animals (group I) served as controls and received oil injections. The two groups were run together on the same pasture and were in other ways treated identically.

Ewes were observed closely around the expected time of lambing. Lambs were weighed within 12 hr after birth and the ewe that had borne each lamb noted.

Statistical significance was tested by  $\chi^2$  and Student's *t* tests.

### RESULTS

Ten normal lambs (4 males, 6 females) were produced by the 10 control ewes in group I (Table 1). Ewes of this breed normally produce 1 lamb per gestation. Only 7 lambs (3 males, 4 females) were born to the 16 T-treated ewes of group II ( $p < 0.05$  by chi-square test). Weights of the 10 lambs from group I ewes were  $5.79 \pm 0.93$  kg (mean ± SD). Weights of the 7 lambs from group II ewes were  $4.00 \pm 0.51$  kg ( $p < 0.01$  by *t* test). Lambs from group II were obviously masculinized (clitoromegaly and partially fused vaginas in the females and adult penile development in the males), but there was no other gross anatomic difference between the lambs of the two groups. Gestation lengths (Table 1) were not significantly different between the two groups.

### DISCUSSION

The results of the present study imply that T administration to pregnant ewes from day 75 to 150 of gestation markedly decreases fetal growth and survival as well as inducing masculinization. Phoenix et al.<sup>3</sup> found "relatively high abortion rates" during T administration to pregnant monkeys, but actual abortion rates and birth weights were not detailed. Beach and Kuehn<sup>4</sup> described a variety of perinatal difficulties including premature delivery in pregnant bitches treated with T. Clarke et al.<sup>5</sup> have recently described a modestly increased rate of fetal death among pregnant ewes receiving T in late gestation; birth weights were not reported. Dehydroepiandrosterone, which has a masculinizing effect on female fetuses, also impairs fetal growth in rats.<sup>6</sup>

Limited clinical data suggest that human fetal growth may be retarded by maternal exposure to androgens. Average weight of 15 female neonates who had been masculinized in utero because their mothers had received androgens was 3013 gm<sup>7</sup> compared to averages at 40 wk gestation of 3280 gm in a large series from the same city,<sup>8</sup> and 3389 gm in normal females from another city.<sup>9</sup> Similarly, Black and Bentley<sup>10</sup> comment on the low birth weight of the female neonate masculinized in utero that they report and mention a similar trend in other case reports in the literature.

The mechanisms through which T affects fetal growth and survival are un-

known. It may be that metabolic products of T are important. It is known that the ovine fetoplacental unit is capable of metabolizing T to estrogens<sup>11</sup> and that estrogens induce fetal growth retardation and abortion in the rat.<sup>12,13</sup> Alterations in the production or metabolism of androgens by the mother or the fetoplacental unit may exert important influences on fetal growth and survival.

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