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EFFECTS OF ESTROGEN AND PROGESTERONE ON PROGESTERONE LEVELS OF CORPORA LUTEA AND ON PREGNANCY IN HEIFERS [1]

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IN cattle, estrogens cause early pregnancy loss and abortion (Rahlmann and Cupps, 1962) and prevent normal function of the corpus luteum (Loy *et al.*, 1960); Wiltbank, 1966). Estrogens have been used extensively to induce abortion in feedlot heifers. The abortion is thought to be due to an unfavorable uterine environment induced by estrogen directly or indirectly through the regression of the corpus luteum. The present study was to determine the effects of a single intramuscular injection of estradiol valerate alone and in combination with daily injections of progesterone on corpus luteum function and maintenance of pregnancy in heifers. The ability of ovaries of pregnant heifers to ovulate and form functional corpora lutea by treatment with chorionic gonadotropin after corpus luteum removal also was examined.

Materials and Methods

Twenty-two heifers, largely of Holstein breeding, that were 35 days pregnant and two Guernsey heifers that were 42 and 68 days pregnant were used in this study. Pregnancy and changes in ovarian activity were determined by rectal palpation of the reproductive organs at regular intervals. The heifers were observed twice daily for estrus throughout the study. Four heifers each were assigned to one of the following treatment groups: (1) control, untreated; (2 and 3) 20 mg. estradiol valerate on day 35 of pregnancy; (4) 100 mg. progesterone daily for 13 to 25 days starting on day 35 of pregnancy; and (5 and 6) combination of estradiol valerate and progesterone treatments. There were two exceptions as groups 3 and 6 included the two Guernsey heifers that were started on treatment on days 68 and 42 of pregnancy, respectively. The heifers in groups 1, 2, 4 and 5 underwent corpus luteum removal through a supravaginal laparotomy on day 38 of pregnancy. Heifers in groups 3 and 6 were not laparotomized but observed and examined for changes in reproductive status up to 25 days after estradiol valerate injection. After pregnancy maintenance with progesterone for 10 days following removal of the corpus luteum, the heifers in groups 4 and 5, plus an additional heifer that had been injected with 10 mg. of estradiol valerate were divided into two new groups (A and B) of four and five heifers, respectively. In group A, the progesterone injection was reduced to 75 mg. on the 48th and 49th day of pregnancy, and in addition, on day 49, 3,000 I.U. of human chorionic gonadotropin (HCG) was injected intravenously. On days 50, 51, 52, 53 and 54 of pregnancy, the heifers received the following respective doses of HCG (intramuscular) and progesterone; 1,000 I.U. and 50 mg.; 1,000 I.U. and 50 mg.; 500 I.U. and 25 mg.; 500 I.U. and 25 mg.; and 500 I.U. and 0 mg. The five heifers of group B received 3,000 and 1,000 I.U. of HCG and 75 and 50 mg. of progesterone on days 48 and 49 of pregnancy, respectively. The injection schedule for days 50 through 54 was the same as for group A except 500 I.U. of HCG was given on day 51.

Physiological saline was the diluent for HCG and sesame oil was the vehicle for the steroid hormones. Estradiol valerate was given as a single intramuscular injection and progesterone was injected daily subcutaneously.

After removal from the ovaries the corpora lutea were immediately weighed and minced into small pieces from which duplicate samples weighing approximately 200 mg. were taken and stored in 95% ethanol at —15° C. for subsequent progesterone analysis. Luteal tissue progesterone and 4-pregnene-20 β-ol-3-one (20 β-ol) were analyzed according to the method outlined by Stormshak *et al.* (1963). The values were corrected for procedural

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TABLE 1. EFFECTS OF ESTRADIOL VALERATE AND PROGESTERONE ON LUTEAL FUNCTION

Treatment group	Corpus luteum wt. (gm.) ±S.E.[a]	Progesterone		Progesterone+20 β-ol	
		Conc. (μg./gm.) ±S.E.	Content (μg./gld.) ±S.E.	Conc. (μg./gm.) ±S.E.	Content (μg./gld.) ±S.E.
1 Control	5.28±.26	60.1±3.8	318.6±27.9	65.9±3.0	349.0±30.1
2 Estradiol valerate	4.25±.42	41.8±3.2	175.6±15.2	45.1±2.2	190.2±15.0
4 Progesterone	5.22±.43	59.0±4.8	294.0±13.8	63.0±7.4	312.2±9.4
5 Est. val. +prog.	4.48±.39	43.1±4.0	193.7±14.6	47.4±5.2	214.0±25.4

[a] S.E.=Standard Error.

losses by the use of labeled progesterone in the chemical analysis. The data were subjected to analysis of variance and the statistical significances of the differences among means were determined by Duncan's new multiple range test.

Results and Discussion

Compared with no treatment and progesterone treatment, estradiol valerate, with and without progesterone, resulted in significant ($P<.05$) and highly significant ($P<.01$) decreases in progesterone concentration and content of corpora lutea, respectively, and tended ($P<.10$) to depress corpora lutea weight (table 1). Kaltenbach *et al.* (1964) reported that a single injection of several estrogens, including estradiol valerate (5 mg.), on day 35 of pregnancy in beef heifers caused decreases in these three parameters of the corpus luteum within 1 week. The 3 days of progesterone treatment of heifers had no apparent effect on corpus luteum weight or on progesterone level in comparison to the control group.

Following removal of corpora lutea, the untreated heifers (group 1) and the estrogen-injected heifers (group 2) returned to estrus on the average of 3.5 and 2.0 days later, respectively. One control heifer and two estrogen treated heifers developed cystic ovaries and nymphomania after returning to estrus. Pregnancy was maintained by progesterone administration in each of the heifers in groups 4 and 5 after corpus luteum removal. Heifers in group 3 (corpora lutea intact) returned to estrus an average of 8.5 days (range 5 to 13 days) after estradiol valerate injection. These heifers were examined rectally on the day of estrus. The uterine horns were enlarged but no evidence of the previous pregnancies was found. Administration of progesterone in conjunction with estrogen maintained the pregnancy in each of the heifers in group 6 until slaughtered at 20 to 23 days after estrogen treatment. The corpora lutea, however, had regressed to less than 12 mm. in diameter by approximately 12 days post-injection of estradiol valerate. These results suggest that estrogen terminates pregnancy primarily through the regression of the corpus luteum. This effect is probably mediated through the hypothalamo-pituitary-ovarian system by the inhibition of the luteal maintaining gonadotropins as luteinizing hormones can overcome the effects of estrogen in heifers (Niswender *et al.*, 1965). It is unlikely that the estradiol valerate exerted any direct detrimental influence on the uterus or conceptus as pregnancies continued normally with daily administration of progesterone.

Attempts with HCG injections to induce new and functional corpora lutea and the subsequent maintenance of the pregnancies that were previously maintained with progesterone treatment were successful in one of four heifers in group A and four of five heifers in group B. Failure to induce ovulation and functional-size corpora lutea appeared to be the cause of the pregnancy loss. Three of the heifers experienced estrus and one heifer had a quiet ovulation within 2 wk. after the initial HCG injection. The pregnant heifers were observed for 1 to 4 mo. after the induction of the new corpora lutea. HCG treatment did not cause multiple ovulation and the induced corpora lutea were of normal size (16 to 22 mm.) in the heifers remaining pregnant.

Summary

A single injection of 20 mg. estradiol valerate was given to eight heifers on day 35 of pregnancy, with half of the group also receiving 100 mg. of progesterone daily. The corpora lutea, removed on day 38, showed significant reduction in the concentration and content of progesterone compared with corpora lutea from four untreated control heifers. Progesterone treatment alone had no effect

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on progesterone level in the corpus luteum. Estradiol valerate alone caused pregnancy loss and estrus in heifers, whereas in combination with daily injections of progesterone the corpora lutea regressed but pregnancy loss and estrus did not occur. Injection of HCG during the progesterone-treatment period of heifers with the corpus luteum removed induced new corpora lutea that maintained pregnancy in five of nine heifers after progesterone withdrawal.

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