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# The Role of Corticoids in Parturition

W. M. ADAMS AND W. C. WAGNER

*College of Veterinary Medicine, Iowa State University, Ames, Iowa*

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Labor was initiated within 72 hr in 46 of 54 cattle treated with 20 mg dexamethasone intramuscularly. Parturition was induced in animals injected as early as 246 days post-conception although the procedure was more effective later than 255 days of pregnancy. Similarly, 10 or 20 mg dexamethasone intramuscularly was effective in initiating labor within 72 hr resulting in parturition in 11 of 23 ewes. Only two of eight ewes injected on days 133–139 lambed within 72 hr postinjection compared to 9 of 15 ewes injected on days 140–142 of pregnancy. Normal gestation length is 148 days for the ewes and 278–288 days for the cattle used in this study. Analysis of peripheral plasma during normal parturition in 10 cows indicated a rise in plasma corticoids on days 4–1 prepartum that was significantly different ($p < .001$) from levels obtained on days 7–5 prepartum or days 3–7 postpartum. This abrupt elevation in maternal plasma corticoids may result from increased synthesis by the fetal adrenals and provide the signal for termination of the pregnancy.

Experimental studies in sheep have indicated the importance of a functional fetal adrenal for normal parturition (Kennedy *et al.*, 1967; Drost and Holm, 1968). Liggins (1968) demonstrated that continuous administration of ACTH or cortisol to ovine fetuses in utero resulted in parturition in 4–7 days. Liggins (1969) has further shown that dexamethasone treatment of the fetus gave similar results while treatment of pregnant ewes at the rate of 4.0 mg dexamethasone per 24 hr did not result in premature delivery. However, Adams (1969) was able to induce premature delivery in cattle with a single dose of dexamethasone (20 mg/cow).

Prolonged pregnancy can occur when the fetal pituitary–adrenal system is nonfunctional (Holm, 1966). Natural occurrence of this condition has been recorded in cattle (Holm *et al.*, 1961), in cyclopian anomalies of sheep (Binns *et al.*, 1962) and in anencephalic fetuses in the human (Rea, 1898; Milic and Adamsons, 1969). Studies on habitual aborter goats (Van Heerden, 1963; Van Rensburg, 1963) have indicated an association between hyperadrenalism and an abortion syndrome.

The present studies were initiated to study the process of inducing parturition by exogenous glucocorticoids and to monitor adrenal function in cattle during induced and natural parturition by means of peripheral plasma corticoid levels.

## MATERIALS AND METHODS

The cattle used for this study were a part of the teaching herds at Iowa State University and were fed and managed according to usual management procedures. Animals used in the induction study were Holstein, Brown Swiss, Angus, and Hereford. Three Holstein and seven Jersey cows were used for the study of plasma corticoids during normal parturition. The sheep (Columbia-cross Western ewes) were bought for this study and maintained under routine housing and feeding conditions. Cattle were bred by both natural service and artificial insemination. Sheep were bred naturally by a marked ram.

Pregnancy examinations were done in the cattle as a routine teaching procedure throughout the year. No pregnancy examinations were attempted in the sheep. The ram was left with the ewes and their individual breeding dates were recorded as the ram marked them.

The amount of dexamethasone[1] used was 20 mg in cattle and 10 mg or 20 mg in sheep. The time of dexamethasone injection in relation to the age of pregnancy in cattle varied from 197 to 293 days post-conception. The normal mean conception-to-parturition interval ranges from 278 ± 5 days for Holsteins to 288 ± 5 days for Brown Swiss. Angus and Hereford cattle are intermediate between these two breeds (McDonald, 1969). Asdell (1946) indicated a gestation period of 148 days for Columbia ewes. Complications of parturition, postpartum recovery, weight and viability of the offspring, and subsequent breeding ability of the induced animals were recorded.

Uterine biopsy specimens were obtained using a Yoeman biopsy punch with a 24-inch handle via the cervix of the cow. Heparinized blood for hormone assays was collected from the cattle at 8-hr intervals via an indwelling jugular vein catheter for 4 days before and 4 days after dexamethasone injection. Blood samples from cows during normal parturition were sampled in like manner, except that the samples were collected at 6-hr intervals throughout the sampling period. Samples were chilled in an ice bath, centrifuged within 1 hr, and the plasma stored at −20C.

Plasma corticoid levels were determined by the protein-binding method of Murphy (1967) as modified by Whipp and Lyon (1970). Briefly this method consisted of extraction of 0.5 ml of plasma with 4.5 ml of methylene chloride. One-milliliter aliquots of the methylene chloride extract were placed in 12 × 75-mm disposable glass assay tubes and dried in a water bath at 45C. To the dried extract in the tube was then added 0.5 ml of distilled water (1 μg EDTA/100 ml) and 0.5 ml of 6% corticoid binding globulin. This mixture was incubated for 5 min at 45C, placed in a water bath at 10C for 10 min. Fifteen milligrams of Fuller's earth were added, the tubes shaken for 1.5 min, placed in the water bath at 10C for 10 min, centrifuged for 1.5 min, and then placed again in the water bath at 10C for 10 min. After this last 10-min incubation in the cold water bath, 0.5 ml of the supernatant fluid was removed and placed in a scintillation vial with 10 ml of scintillation fluid and counted in a Beckman LS-100 counter. The procedure has been verified by assaying plasma from hypophysectomized calves containing known added amounts of cortisol and/or corticosterone.

## RESULTS

*Cattle.* The results of parturition induction in cattle are shown in Table 1. Forty-six of the 54 animals were successfully induced. A successful induction was defined as one in which labor was initiated within 72 hr from the time of dexamethasone injection resulting in parturition. The mean interval to fetal expulsion was 49 hr after dexamethasone injection with a range of 22–80 hr.

The difference of time between the start of obvious labor and parturition was usually small, averaging about 2 hr. Premonitory signs were minimal. Ten cows required assistance during delivery, repositioning of the fetus being the usual problem, although one cesarotomy was performed

Eight of the 54 animals were considered failures because labor was not initiated within the 72-hr period. Five of the eight did calve within 10 days and the three remaining animals delivered calves 27, 36, and 66 days after dexamethasone. The mean age of pregnancy for the successes was 274 days with a range of 250–293 days. The mean age of pregnancy

TABLE 1
PARTURITION INDUCTION IN CATTLE WITH DEXAMETHASONE

| Day of pregnancy at injection | No. animals | Induced | | | Not induced (no. animals) |
|---|---|---|---|---|---|
| | | No. animals | Interval to fetal expulsion (hr) | | |
| | | | Mean | S D | |
| 275+ | 27 | 25 | 47.3 | 14.5 | 2 |
| 265–274 | 8 | 7 | 44.7 | 14.0 | 1 |
| 255–264 | 12 | 11 | 52.7 | 14.3 | 1 |
| 245–254 | 5 | 3 | 61.3 | 16.3 | 2 |
| <245 | 2 | 0 | | | 2 |
| | 54 | 46 | | | 8 |

for the nine failures was 254 days with a range of 197–289 days. There were three stillborn calves from the 54 animals; all were in the failure group. As can be seen in Table 1, the procedure was quite effective as early as 255–264 days of pregnancy. However, only three of seven animals treated earlier than this calved in response to the dexamethasone.

A major side effect of this procedure in cattle is the retention of fetal membranes and concomitant endometritis. Twenty-seven of the 46 animals in which parturition was induced had retained fetal membranes. Histologic examination of uterine biopsy specimens which were obtained 14–19 days postpartum from 24 of the treated cows, indicated at least a mild degree of inflammation beyond the normal postpartum changes. However, other parameters of uterine involution, such as epithelial regeneration, seemed to be normal.

Five cows were given an oral progestin (6-chloro-17-acetoxy progesterone) during the induction period; they had less severe placental retention problems and postpartum metritis and all five were again pregnant in 60–90 days. Only 16 of the remaining 41 induced animals became pregnant in the subsequent 90-day period.

Assay of plasma corticoids in seven pregnant cows treated with 20 mg dexamethasone showed an average daily pretreatment level of 5–11 ng/ml compared to less than 1 ng/ml after treatment (Fig. 1). The marked depression of plasma corticoids lasted at least 2 days after the single injection of dexamethasone. This depression of endogenous steroid level lasted for 4 days in three of the seven cows. Results of all samples for each 24-hr period were pooled to give a mean daily value for each animal. It was felt that this would give a more meaningful picture since there is rather wide variation from sample to sample due to uncontrollable environmental factors acting on the animals.

The results of analysis of peripheral plasma for corticoids during normal parturition are

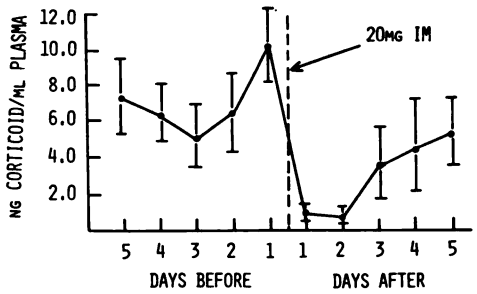


FIG. 1. Effect of 20 mg Dexamethasone on plasma corticoid levels in seven pregnant cows. The values given are means ± SE.

shown in Fig. 2. Day 0 was the 24-hr period represented by 12 hr before and after parturition. All other days were then calculated from this time in 24-hr intervals regardless of time of day. These results were pooled by day to give a single daily value for the reasons previously discussed. The 10 animals sampled exhibited a significant rise in corticoid levels during the last 4 days prior to parturition when compared to values obtained on days 5–7 prepartum and days 3–7 postpartum ($t = 4.81$, $df = 77$, $p < .001$). Not all animals were sampled for 7 days prepartum due to the problem of predicting time of calving.

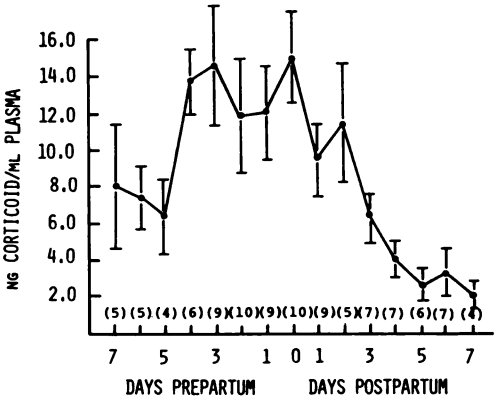


FIG. 2. Plasma corticoid levels before, during and after normal parturition in the cow. Numbers in parenthesis indicate number of animals sampled on each day. Day O is parturition ± 12 hours. The values given are means ± SE.

TABLE 2
PARTURITION INDUCTION IN SHEEP WITH DEXAMETHASONE

| Day of pregnancy at injection | No. animals | Induced | | | Not induced (no. animals) |
|---|---|---|---|---|---|
| | | No. animals | Interval to fetal expulsion (hr) | | |
| | | | Mean | S D | |
| 140–142 | 15 | 9 | 43 | 4 | 6 |
| 138–139 | 4 | 1 | | | 3 |
| 133–137 | 4 | 1 | | | 3 |
| | 23 | 11 | | | 12 |

*Sheep*. The results of the sheep are shown in Table 2. Both the 10-mg and 20-mg dosage gave similar results. Eight of 15 ewes receiving 10 mg dexamethasone and three of eight ewes given 20 mg dexamethasone lambed within 72 hr. All other ewes lambed from 5–18 days after treatment. The mean age of pregnancy for induced and noninduced ewes was not significantly different (141 vs 138 days). However, only two of eight ewes treated before day 140 of pregnancy lambed within the 72-hr period compared with 9 of 15 ewes treated at 140–142 days of pregnancy.

There were no retained fetal membranes in the sheep nor was there any obvious metritis. However, since none of the ewes was held for breeding the next year their subsequent fertility was not evaluated. Although there were no stillborn lambs, many were small and required extra nursing care to get them started. The 23 ewes gave birth to 34 lambs, of which 24 were weaned and marketed.

## DISCUSSION

Liggins (1968, 1969) has shown that fetal infusion of cortisol would initiate parturition but was not able to cause premature parturition by injection of 4 mg dexamethasone per ewe per day. Our data indicate that parenteral treatment of the maternal organism is sufficient in some species if appropriate amounts are used. Since rate of induction failure increased as the dexamethasone was injected earlier in pregnancy, the mechanism apparently becomes more sensitive as the fetus approaches maturity. This would seem logical as a protective device to prevent interruption of pregnancy in natural stress situations. Also, the time period from dexamethasone injection to fetal expulsion tended to increase in those animals injected earlier in pregnancy.

The precipitous drop in plasma corticoid levels in the treated cows indicates 20 mg of dexamethasone was sufficient to block corticotropin release from the pituitary and/or adrenal secretion of steroids for 2 days in four cows and 4 days in three cows. This dosage results in above normal blood levels of corticoid-like activity in the treated animals and is pharmacologic in amount.

Prevention of parturition by fetal adrenalectomy in sheep (Drost and Holm, 1968) and the corticoid and ACTH infusion studies of Liggins (1968, 1969) indicate an important role for the adrenal in initiation of parturition. Several authors have shown that fetal adrenals in various species are capable of synthesizing cortisol and/or corticosterone (Jackson and Piasecki, 1969; Milkovic and Milkovic, 1962; Chouraqui and Weniger, 1968; Kamoun and Stutinsky, 1968). Abramovich and Wade (1969a) have reported a linear increase in amniotic fluid content of 17-hydroxycorticosteroids during pregnancy in women. They concluded that this represented an increasing output in steroids from the adrenals of the fetus. Kamoun and Stutinsky (1968) have shown that there is a measurable corticoid level in maternal plasma at 18 and 20 days of pregnancy in adrenalectomized rats. They

concluded that the hormones originated from the fetal adrenal. Although Voogt *et al.* (1969) did not observe a rise in plasma corticosterone during late pregnancy in intact rats, more frequent samples may be needed to detect such a change. Bassett and Thorburn (1969) demonstrated a rise in corticosteroids in ovine fetal plasma just prior to parturition, but did not detect any concomitant rise in maternal plasma corticosteroids.

Dassler (1967) found an increase in urinary excretion of 11-deoxycorticoids in late pregnancy that was not present in cases of fetal death, and it therefore seems likely that these intermediate products indicate an increase in fetal adrenocortical activity. Thus, the increase in fetal output and amniotic fluid content reported by other workers may be sufficient to spill over into the maternal circulation as shown by Kamoun and Stutinsky (1968) in the rat. Abramovich and Wade (1969b) have demonstrated in humans that cortisol is able to cross the placental barrier from the maternal to the fetal side. Although definitive proof is lacking, the rise in plasma corticoids seen just prior to parturition in the cow may be the result of an increase in steroid secretion by the fetal adrenal system with transport across the placenta to the maternal circulation. Whether corticoids cross the placenta from fetus to dam needs to be resolved on a species by species basis.

This increase in maternal plasma corticoids appears to be different from that observed in the human during the last 1–3 months of pregnancy (Stewart *et al.*, 1961; Friedman and Beard, 1966). They reported a gradual corticoid increase reaching two to three times the normal level in late pregnancy. It is primarily due to an increase in the amount of binding protein in the plasma (Doe *et al.*, 1964; DeMoor *et al.*, 1966). The increase observed in this study was of short duration lasting only 3–5 days prepartum and was abrupt in onset. We do not feel that this observation is comparable to the phenomenon seen in the human during the last trimester.

Habitual aborter Angora goats have a markedly higher cortisol secretion rate in response to ACTH than normal goats. In addition, the aborted fetuses had hyperplastic adrenals and atrophy of the thymus (Van Rensburg, 1965). Van Heerden (1963) stated that the Angora does aborted due to failure of the corpus luteum. Brunner *et al.* (1969) have reported that ACTH injections can depress CL formation in the cow.

Furthermore, adrenal hyperfunction may cause CL failure in the goats as Van Heerden (1963) has suggested. Thus, the prepartum rise in plasma corticoids seen in the cows in this study may cause a decline in CL function and serve to initiate parturition. However, we are unable to explain how this mechanism might work in a species in which the CL is not needed for maintenance of pregnancy, e.g., human, mare. Administration of 20–40 mg dexamethasone in 10 mares (six of them pony size) during the last month of pregnancy did not cause premature parturition in any animals. (W. M. Adams, unpublished data).

We believe that the use of exogenous corticosteroids for artificial induction of parturition may serve as a useful experimental model to determine mechanisms involved in the initiation of parturition. Additionally, it may become a useful method of controlling parturition in ruminants that have previously been bred at a controlled ovulation.

[1] 9-alpha-fluoro-16-alpha methylprednisolone.

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