Evidence for reset of regulated cortisol in pregnancy: studies in adrenalectomized ewes

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Keller-Wood, Maureen. Evidence for reset of regulated cortisol in pregnancy: studies in adrenalectomized ewes. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R145–R151, 1998.—These studies test the hypothesis that the increased adrenocorticotropic hormone (ACTH) and cortisol in pregnancy reflect a reset of regulated plasma cortisol concentrations. Ewes were sham operated (Sham) or adrenalectomized (ADX) at ~108 days gestation. Adrenalectomized ewes were replaced with aldosterone (3 μg·kg⁻¹·day⁻¹) and with cortisol at either of two doses (ADX + 0.6 mg·kg⁻¹·day⁻¹; the ewes were also studied postpartum. Plasma cortisol concentrations in ADX + 0.6 ewes (5.3 ± 1.3 ng/ml) were similar to the Sham ewes postpartum (5.5 ± 0.6 ng/ml), whereas ADX + 1.0 concentrations (8.9 ± 1.0 ng/ml) were similar to pregnant Sham ewes (9.5 ± 1.9 ng/ml). Plasma ACTH concentrations were significantly increased in the pregnant ADX + 0.6 ewes (273 ± 44 pg/ml) relative to pregnant Sham ewes (84 ± 9 pg/ml) or the same ewes postpartum (42 ± 9 pg/ml). Plasma ACTH concentrations were not different among the groups postpartum. Acute increases in plasma cortisol to 15–25 ng/ml produced similar inhibition in all groups. These results suggest that pregnancy resets the basal cortisol concentration required for normalization of basal ACTH concentration.

adrenocorticotropic hormone; corticotropin; glucocorticoid; mineralocorticoid; feedback

DURING PREGNANCY IN SEVERAL SPECIES, including humans and sheep, maternal plasma cortisol concentrations approximately double (10, 13, 17). The increase in free cortisol concentrations is caused by an increase in adrenal response to adrenocorticotropic hormone (ACTH) (17) and an increase in plasma ACTH concentrations; plasma ACTH concentrations increase over time during human pregnancy (7, 23), and when after-noon plasma ACTH concentrations in pregnant women are compared with those in nonpregnant women, they are found to be significantly increased (7).

Several studies in pregnant women suggest that the control of ACTH by glucocorticoids is altered in pregnancy (17). In women, dexamethasone treatment does not completely suppress plasma cortisol concentrations (8, 18); however, because the clearance of synthetic glucocorticoids and the adrenal responsiveness to ACTH are increased in pregnancy (17, 30), the failure to completely inhibit urinary and plasma cortisol may also reflect these factors. Betamethasone treatment has been shown to reduce both plasma ACTH and cortisol concentrations (28) in pregnant women, although suppression is also not complete. It was found that when plasma cortisol is infused into pregnant ewes, plasma ACTH levels are suppressed (13). Increases in cortisol to 20–40 ng/ml, levels similar to those produced by stress, inhibit both basal, unstimulated ACTH secretion and stimulated ACTH secretion. The inhibition of ACTH by increased cortisol in pregnant ewes is equal to the inhibition of ACTH in nonpregnant ewes, suggesting that the feedback effectiveness of increased cortisol in suppressing ACTH is not altered in pregnancy.

In pregnant ewes, we also observe, however, that plasma ACTH is increased by ~10 pg/ml despite the significantly increased resting cortisol concentrations. This suggests that the feedback effect of lower cortisol concentrations may be altered. We hypothesized that the set point for basal cortisol, and therefore the levels of basal ACTH, is increased in the pregnant state. This hypothesis was tested using a model in which plasma cortisol in pregnant ewes was decreased to levels within the range measured in nonpregnant ewes. If the hypothesis is correct, this manipulation should partially open the feedback loop between cortisol and ACTH and result in an increase in ACTH secretion in the pregnant ewe.

METHODS

Ewes were brought to the Health Sciences Center and subjected to surgery on days 106–114 of gestation (normal term 148–150 days). This facility is accredited by the American Association for Laboratory Animal Care; all experimental procedures involving animals were approved by the University of Florida Institutional Animal Care and Use Committee. Ewes were fasted for 20–24 h, and water was withheld for ~12 h before surgery. Surgery was performed under halothane anesthesia (1–2.5% in O2) after induction with ketamine (20 mg·kg⁻¹ im) and atropine (0.1 mg·kg⁻¹ im). Adrenalectomy was performed with the ewe in sternal recumbency using bilateral flank incisions. Maternal femoral artery and vein catheters were then placed with the ewes in dorsal recumbency as previously described (2). Ewes were assigned to one of three groups: 1) sham adrenalectomized (Sham ADX, n = 4), 2) adrenalectomized with replacement of ~0.6 mg·kg⁻¹·day⁻¹ cortisol to produce levels similar to normal nonpregnant levels (ADX + 0.6, n = 6), and 3) adrenalectomized with replacement of ~1 mg·kg⁻¹·day⁻¹ cortisol to produce levels similar to normal pregnant levels (ADX + 1.0, n = 5). In the ADX + 1.0 group, two adrenalectomized ewes were replaced using intravenous infusions of cortisol hemisuccinate at 50–60 mg/day. Because severe Addisonian crisis and death resulted from interruption of the delivery of cortisol in one of these ewes, the remaining ewes in both ADX groups were replaced using pellets of cortisol implanted subcutaneously outside the scapulae. Pellets containing cortisol hemisuccinate (4–8 pellets, 200 mg cortisol each, released over 21 days to produce release rates of ~0.6–1 mg cortisol·kg⁻¹·day⁻¹). Innovative Research, Sarasota, FL) were placed at surgery and replaced at 21-day intervals throughout the study. Sham adrenalectomies consisted of positioning the ewe in sternal recumbency, placing bilateral flank incisions, locat-
ing the adrenal gland and its surrounding vasculature on each side, and suturing the incisions. Both cortisol and aldosterone treatment doses were chosen based on estimated production rates in pregnant ewes.

All ewes were treated with Polysulf (ampicillin, 750 mg im) two times per day for 5 days postoperatively and one time per day thereafter. Ewes were also treated with Banamine (flu- nixin meglumine, 1 mg/kg im, 1 or 2 times per day) for 1–3 days as necessary for relief of postoperative pain. Adrenalectomized ewes were also treated with 2 µg·kg⁻¹·day⁻¹ of aldosterone hemisuccinate (3 µg·kg⁻¹·day⁻¹) at the end of surgery and continuing throughout the study. Adrenalectomized ewes were also treated with 2 µg·kg⁻¹·min⁻¹ of cortisol hemisuccinate for the first 36–20 h postoperatively; this rate was decreased to 1.0 µg·kg⁻¹·min⁻¹ for the next 24 h. In the first two ewes studied, this rate was decreased to 0.7 µg·kg⁻¹·min⁻¹ (equivalent to 1 mg·kg⁻¹·day⁻¹); in the remaining ewes, in which cortisol was replaced by subcutaneous pellets, the cortisol infusion was terminated. Ewes were monitored daily, and plasma samples were collected to analyze plasma electrolytes, glucose, plasma proteins, and hematocrit.

After recovery from surgery, ewes were then studied in three experiments designed to test the negative feedback relationship between plasma cortisol and ACTH. Plasma ACTH, cortisol, plasma hematocrit, plasma proteins, and electrolytes were measured at 0, 1, 2, 4, 6, and 8 h in each of the three experiments: control replacement (or no replacement in the case of Sham ewes), infusion of 1.4 µg·kg⁻¹·min⁻¹ cortisol, and infusion of 2.0 µg·kg⁻¹·min⁻¹ cortisol. All experiments were begun between 8:30 and 9:30 AM. Because of loss of some ewes, not all of these experiments were performed in all ewes; four to six ewes were studied with each of these acute cortisol infusion experiments in pregnant ewes.

When possible, ewes were also studied after delivery. A total of 12 ewes, 4 per group, were studied postpartum at the control or maintenance cortisol replacement doses. However, loss of catheters or animals resulted in only three ewes in a few groups during infusions of cortisol (Sham with 1.4 or 2 µg·kg⁻¹·min⁻¹, ADX with 0.6 with 2 µg·kg⁻¹·min⁻¹, ADX with 1.4 µg·kg⁻¹·min⁻¹). Because these infusions produced similar degrees of inhibition of ACTH in all the groups postpartum, there were no additional ewes added to the study to replace these animals.

Assays. Blood collected for measurement of plasma ACTH and cortisol was collected into tubes containing 0.015 M EDTA; samples for measurement of plasma electrolytes and hematocrit were collected in tubes containing heparin, and samples for glucose measurement were made into tubes containing sodium fluoride and potassium oxalate. Samples were placed on ice and then spun for 20 min at 2,000 revolutions/min in a refrigerated centrifuge. Aliquots of plasma were frozen for analysis of ACTH and cortisol by radioimmunoassay.

One milliliter of each blood sample was placed in a heparinized tube for determination of plasma sodium and potassium concentration (Nova 1; Nova Biomedical, Waltham, MA). Plasma protein concentrations were measured using a refractometer. Hematocrit measurements (%packed cell volume) were performed on duplicate samples of blood collected in microcapillary tubes and spun for 3 min at 12,000 revolutions/min (Damon Division, International Equipment, Needham Heights, MA). Hematocrit was read to the nearest 0.5%. Glucose measurements were made using a Yellow Springs Instruments glucose analyzer (Yellow Springs, OH). Plasma proteins were read using a refractometer to the nearest 0.1%.

ACTH and cortisol assays were performed as previously described (2), using antibodies to ACTH-(1–24) and cortisol that were produced in this laboratory. The ACTH assay was performed after extraction of the plasma on glass (Corning, Corning, NY) and elution with 1:1 0.25 N HCl and acetone. An aliquot of human ACTH-(1–39) standard was also extracted and used in the assay to correct for recovery.

Analyses. Mean hormone, electrolyte, protein, glucose, and hematocrit data were analyzed by analysis of variance (34). The ACTH and cortisol data were compared among groups for cortisol infusions by analysis of variance corrected for repeated measures across cortisol infusion doses and time. The ACTH data was log transformed before analysis. The hormone, electrolyte, and plasma protein data were also analyzed by linear regression analysis to determine the relationship between plasma cortisol levels and these variables. The slope and intercept of the relationships between cortisol and ACTH were compared by t-test (36). For all statistical analysis, the criterion for significance was P < 0.05.

RESULTS

Basal levels of electrolytes. If steroid replacement was interrupted because of problems with the intravenous catheter or pump, increases in plasma potassium, protein, and hematocrit resulted. However, during treatment with 3 µg aldosterone·kg⁻¹·day⁻¹, along with either 0.6 or 1.0 mg cortisol·kg⁻¹·day⁻¹, values of sodium, potassium, plasma proteins, and hematocrit were within the normal range in all groups, suggesting that all replacement regimes prevented disruption of electrolyte balance in these ewes (Table 1). Mean arterial pressures were also in the normal range in all ewes (data not shown).

Table 1. Values of plasma Na⁺, K⁺, protein, and glucose concentrations at maintenance replacement dose

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Na⁺, meq/l</th>
<th>K⁺, meq/l</th>
<th>Protein, mg/100 ml</th>
<th>Glucose, mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>4</td>
<td>147.3 ± 0.8</td>
<td>4.70 ± 0.10</td>
<td>7.4 ± 0.9</td>
<td>56 ± 1</td>
</tr>
<tr>
<td>ADX + approx. 1.0 mg·kg⁻¹·day⁻¹</td>
<td>5</td>
<td>145.3 ± 1.5</td>
<td>5.50 ± 0.73</td>
<td>8.2 ± 0.3</td>
<td>64 ± 1</td>
</tr>
<tr>
<td>ADX + approx. 0.6 mg·kg⁻¹·day⁻¹</td>
<td>6</td>
<td>148.3 ± 1.1</td>
<td>4.59 ± 0.30</td>
<td>7.5 ± 0.3</td>
<td>56 ± 6</td>
</tr>
<tr>
<td>Postpartum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>4</td>
<td>145.6 ± 1.6</td>
<td>4.51 ± 0.10</td>
<td>8.3 ± 0.3</td>
<td>57 ± 2</td>
</tr>
<tr>
<td>ADX + approx. 1.0 mg·kg⁻¹·day⁻¹</td>
<td>4</td>
<td>150.0 ± 0.8</td>
<td>3.94 ± 0.18</td>
<td>8.6 ± 0.4</td>
<td>65 ± 7</td>
</tr>
<tr>
<td>ADX + approx. 0.6 mg·kg⁻¹·day⁻¹</td>
<td>4</td>
<td>149.9 ± 0.9</td>
<td>4.07 ± 0.18</td>
<td>8.3 ± 0.4</td>
<td>66 ± 3</td>
</tr>
</tbody>
</table>

Data are mean values of samples taken over 8 h of sampling at control or maintenance dose. Sham, sham operated; ADX, adrenalectomized.
The results of the regression analyses indicated some relationships between cortisol levels and plasma sodium and potassium concentrations. There was a weak but significant positive relationship between plasma cortisol and plasma sodium concentrations in the pregnant Sham and in the nonpregnant ADX ewes (r = 0.20 and 0.19, respectively). The relationship between plasma cortisol and plasma potassium was also significant in the nonpregnant ADX ewes (r = −0.20). However, the relationship between plasma cortisol and plasma potassium was only significant in the pregnant ADX ewes (r = 0.17).

Basal ACTH and cortisol. There was a significant effect of the steroid treatment dose on plasma cortisol and on plasma ACTH concentrations (Fig. 1). The cortisol concentrations in Sham ewes were significantly greater during pregnancy than postpartum. Over the course of the study, the ADX + 0.6 ewes had plasma cortisol concentrations similar to those in Sham ewes postpartum, whereas the ADX + 1.0 ewes had plasma cortisol concentrations similar to those in the Sham ewes during pregnancy. The cortisol concentrations in the ADX + 0.6 ewes were significantly lower than the concentrations in either the ADX + 1.0 or Sham ewes during pregnancy.

The lower plasma cortisol levels in the ADX + 0.6 ewes during pregnancy significantly increased plasma ACTH concentrations compared with the Sham or ADX + 1.0 ewes during pregnancy (Fig. 1A). However, the plasma ACTH levels in the ADX + 0.6 ewes during pregnancy were also higher than in the same ewes postpartum or the Sham or ADX + 1.0 ewes postpartum.

Feedback effects of increases in plasma cortisol. Plasma cortisol was increased by infusion of cortisol at 1.4 or 2 µg·kg⁻¹·min⁻¹ infusion in all groups, and the increases in plasma cortisol were related to the rate of cortisol infusion over the 8 h (Fig. 2). However, there were no significant differences between the concentrations of cortisol achieved by the 8-h infusions of cortisol at 1.4 or 2 µg·kg⁻¹·min⁻¹. There was also no difference in levels of cortisol produced by these infusions among the three treatment groups or between pregnant and nonpregnant conditions.

Plasma ACTH was significantly decreased by infusion of cortisol in all groups of ewes (Fig. 3). There was no significant effect of pregnancy or of the steroid replacement dose on the concentrations of ACTH at 2–8 h after the start of the infusions of cortisol. However, because there were significant differences in initial ACTH and cortisol concentrations, there was a significant effect of pregnancy on the ACTH levels in the control experiment with no added infusion of cortisol and significant interactions between pregnancy and time on the decrease in ACTH in response to the infusions of cortisol.

Relationship between cortisol and ACTH. Plasma ACTH levels were significantly related to plasma cortisol in both ADX and Sham ewes during pregnancy and in Sham ewes postpartum. Plasma ACTH concentrations were significantly related to the plasma cortisol concentrations in ADX ewes during pregnancy but not in postpartum state (Table 2). When data from both ADX and Sham ewes were analyzed, the relationship was significant in both pregnant and nonpregnant ewes; however, the slope of the relationship was significantly greater in the ewes during pregnancy than in the same ewes postpartum. When only the values at 8 h were analyzed, the relationship between plasma cortisol and plasma ACTH was only significant in the ADX ewes during pregnancy (r = −0.56). The significant relationship between plasma cortisol and plasma ACTH in the ADX ewes during pregnancy primarily reflects the relatively high plasma ACTH levels in these ewes at low plasma cortisol levels that are less than the
normal cortisol levels during pregnancy. The lack of significant relationship between ACTH and cortisol in the nonpregnant ewes reflects the low plasma ACTH levels measured in all the nonpregnant ewes; without any added infusion of cortisol above the endogenous levels in the Sham ewes or with the maintenance delivery rate in the ADX ewes, ACTH levels were relatively low in most ewes (Figs. 2 and 3).

The difference in the cortisol-ACTH relationship between pregnant and postpartum states is most striking at plasma cortisol levels less than normal pregnant levels, that is, levels of <5 ng/ml (Fig. 4). If plasma cortisol concentrations in adrenalectomized ewes were maintained at 2–5 ng/ml, a range that is normal for postpartum ewes but abnormally low for pregnant ewes, plasma ACTH levels were markedly increased during pregnancy; however, plasma ACTH levels were generally <100 pg/ml in the same ewes maintained at these plasma cortisol levels postpartum. Plasma ACTH concentrations were <200 pg/ml postpartum in all groups of ewes, regardless of the plasma cortisol concentrations. Plasma ACTH concentrations were 110–500 pg/ml in pregnant adrenalectomized ewes if cortisol concentrations were <5 ng/ml.

**DISCUSSION**

Pregnancy significantly alters the regulation of plasma ACTH levels at low circulating plasma cortisol concentrations. When plasma cortisol concentrations in pregnant ewes are maintained at levels that are lower...
than for pregnant ewes (although within the normal range for nonpregnant ewes), plasma ACTH concentrations are significantly increased. The same level of cortisol does not increase plasma ACTH postpartum. The results suggest that the set point for regulation of plasma cortisol is increased during pregnancy.

Pregnancy did not alter the suppression of ACTH by acute increases in cortisol to concentrations above the normal range of basal levels. During infusions of cortisol to levels similar to those produced by stressors in the ewe, 15–30 ng/ml, ACTH was suppressed in both pregnant and nonpregnant ewes. This result agrees with the results we had previously reported. In previous studies, we found that increased cortisol concentrations decrease basal ACTH and hypotension-stimulated increases in ACTH in pregnant ewes and in nonpregnant ewes and that the degree of suppression of ACTH was not significantly reduced by pregnancy (13). These results suggest that the increase in ACTH is not simply the result of reduced glucocorticoid feedback effects during pregnancy.

We previously found that basal plasma ACTH concentrations in pregnant ewes are significantly greater in pregnant ewes than in noncycling or anestrous ewes (2). Plasma ACTH levels also tend to be greater than in nonpregnant ewes sampled randomly in the estrous cycle in the nonpregnant state (13), and plasma cortisol concentrations are significantly increased (by ~100%) in the pregnant ewe. The results of the present study suggest that this increase in basal ACTH reflects an altered set point for basal plasma cortisol during pregnancy.

We might have expected that the chronic increase in basal cortisol in pregnancy or the higher plasma cortisol in the ADX + 1.0 ewes as compared with the ADX + 0.6 ewes would result in a decreased sensitivity to glucocorticoid feedback. It has been found that chronic exposure to increased cortisol can decrease the expression of the glucocorticoid receptors (4, 12); this effect can be demonstrated both in vivo and in vitro. Our results suggest that the doubling of basal cortisol in pregnancy is not sufficient to alter the feedback effects of increased glucocorticoids, which would be expected to be mediated by the glucocorticoid receptor.

The difference in the effectiveness of decreased cortisol to increase the ACTH concentrations in pregnant ewes relative to nonpregnant ewes, compared with the lack of a difference in the effectiveness of increased cortisol in decreasing ACTH concentrations, could be explained by different mechanisms for feedback control of ACTH by the low and high levels of corticosteroids or by differences in stimulatory factors at low cortisol concentrations between pregnant and nonpregnant ewes. We have measured variables that would indicate changes in several of these stimulatory factors in these ewes; we found no significant differences in basal values of arterial blood pressure, plasma proteins, hematocrit, electrolytes, or glucose in the ewes. This would suggest that the aldosterone replacement dose was sufficient to prevent hypotension, hypovolemia, hypotension, hyperkalemia, or hypoglycemia. However, if the aldosterone dose was not delivered, or, in the two ewes in which cortisol was replaced by intravenous infusion, if the cortisol delivery was inadvertently interrupted (by pump disconnection, kinking of the intravenous catheter, or power failure), then the adrenalectomized ewes suffered from severe hypotension, hypovolemia, and hyperkalemia. Thus, although corticosteroids were essential for homeostasis in the ewes, the ewes appear to be able to maintain adequate maternal pressure and electrolyte balance, given an adequate supply of food, salt, and water and even relatively low replacement doses of cortisol and aldosterone. However, unlike rodents, the ewes do require some steroid replacement to prevent Addisonian crisis. For this reason, we switched from replacement of cortisol by intravenous infusion to cortisol replacement by subcutaneously placed pellets.

It is known that a dual system for sensing corticosteroids exists in the brain, pituitary, and many peripheral tissues. In the rat, corticosterone binds to both mineralocorticoid (or corticosteroid type I) and glucocorticoid (or corticosteroid type II) receptors. In the rat, the

### Table 2. Summary of results of correlation between logarithm of plasma cortisol and logarithm of plasma ACTH concentrations

<table>
<thead>
<tr>
<th>Group of Ewes</th>
<th>n</th>
<th>Intercept</th>
<th>Slope</th>
<th>Correlation Coefficient (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td>217</td>
<td>2.58</td>
<td>-0.633</td>
<td>-0.48*</td>
</tr>
<tr>
<td>Postpartum</td>
<td>173</td>
<td>1.65</td>
<td>-0.04</td>
<td>-0.05</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td>306</td>
<td>2.4</td>
<td>-0.503</td>
<td>-0.43*</td>
</tr>
<tr>
<td>Postpartum</td>
<td>250</td>
<td>1.77</td>
<td>-0.117</td>
<td>-0.06</td>
</tr>
</tbody>
</table>

Relationships in nonpregnant ewes are not statistically significant. Data from 0- to 8-h experiments in both groups of ADX ewes or experiments in all ADX and Sham ADX ewes were used for analysis. ACTH, adrenocorticotropic hormone. *P < 0.05.
mineralocorticoid receptors (MR) are relatively high-affinity, low-capacity corticosterone binding sites, whereas the glucocorticoid receptors are lower-affinity, but higher-capacity sites in most tissues, including brain and pituitary (24, 26). Although these receptors have not been characterized in sheep, it is known that in the dog, another species that primarily secretes cortisol, the MR appears to have a high affinity for cortisol (25). It has been suggested that regulation of ACTH by low levels of corticosteroids, within the range of the normal basal levels, is mediated by mineralocorticoid (or type I) receptors and that the regulation of ACTH by stimulated corticosteroids is mediated by glucocorticoid (or type II) receptors (9, 26). If this pattern also holds for the sheep, then the decrease in regulation by low cortisol concentrations, but not by high cortisol levels, could reflect a change in MR in the brain or pituitary in pregnancy.

There is evidence in nonpregnant rats that ovarian steroids may alter regulation of ACTH and may alter cortisol feedback regulation of ACTH. Estrogens appear to increase ACTH responses to stress (3, 28, 32) and to decrease the fast-feedback effect of corticosteroids (22). Effects of progesterone are less clear; however, progesterone appears to decrease the availability of MR (5, 6). Progesterone is known to be a mineralocorticoid antagonist (14, 33); recent evidence suggests that progesterone might also alter mineralocorticoid expression. Progesterone inhibits transcription of MR in cultures (16) through a progesterone receptor-mediated effect and decreases the percentage of cells that concentrate aldosterone in the nuclei (15), suggesting fewer cells had available receptors for binding. Treatment of rats with progesterone resulted in an increase in the apparent dissociation constant of MR in hippocampus 4 h later, indicating progesterone competition for MR; however, there was no change in mRNA for MR with this duration of exposure (5, 6). A decrease in MR number or affinity could explain the effect of pregnancy found in our studies; however, further characterization of ovine steroid receptor binding affinities and of changes in receptor number, affinity, and availability in the pregnant state will be necessary to determine if this mechanism explains our results.

Perspectives

A reset of the maternal pituitary-adrenal axis appears to result in the maintenance of chronically elevated maternal cortisol levels in pregnancy. This occurs without desensitization of the glucocorticoid feedback mechanism to increased cortisol. This results in a chronic doubling of maternal cortisol without the production of a state of pronounced hypercorticism. The results suggest that during pregnancy the axis is reset to chronically produce approximately two times the normal plasma cortisol levels. It is not known what role the increased plasma cortisol might play in the normal physiology of pregnancy. It is known that the maternal adrenal is responsible for up to 98% of the circulating fetal cortisol before the fetal adrenal gland itself starts producing cortisol; in most species, fetal adrenal maturation occurs relatively late in gestation (35). Therefore, the increased maternal secretion of cortisol may be important to maintain fetal vascular reactivity or volume in the period before fetal adrenal development. The mother also may require increased cortisol for the normal increase in maternal fluid volume and decrease in glucose utilization. In women, either hypercorticism or hypocorticism can result in an increased incidence of fetal growth retardation, prematurity, and fetal or neonatal death (20, 21). Addison’s disease presenting in pregnancy has deleterious outcomes for both mother and fetus (11, 19, 29), although women with diagnosed Addison’s disease can be adequately managed with increased steroid treatment (1). Although we did not observe obvious disturbances in maternal glucose or electrolytes in the ewes maintained at lower levels of cortisol, so long as aldosterone replacement and food and water intake were maintained, we did observe an increased incidence of abortion and fetal death in these ewes (data not shown). We hypothesize that the elevation of maternal cortisol may therefore be essential for normal fetal development and homeostasis.

I thank Sara Caldwell for her excellent technical assistance with the care of these animals and Dr. Charles E. Wood for his expert surgical skills in performing the adrenalectomies.

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REFERENCES


CONTROL OF ACTH BY CORTISOL DURING OVINE PREGNANCY