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# Fetal and Maternal Corticosterone and Corticosteroid Binding Globulin in the Diabetic Rat Gestation

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**ABSTRACT. Delayed fetal lung development is a feature of the diabetic pregnancy. Since fetal glucocorticoids are important in the regulation of lung maturation, we measured corticosterone and corticosteroid-binding globulin binding capacity in streptozotocin-diabetic pregnant rats and their fetuses. Previous studies have demonstrated delayed fetal lung maturation in this animal model. In control fetuses, total corticosterone concentration increased through day 20 of gestation, then declined until day 22 (term). The unbound steroid, which accounted for 5–10% of the total, increased approximately 3-fold from day 18 to term. Corticosteroid-binding globulin binding capacity peaked on day 19 after which it decreased. Maternal total and unbound corticosterone levels and corticosteroid-binding globulin binding capacity remained relatively constant throughout the final week of normal gestation. When compared to controls, fetuses from diabetic pregnancies had significantly lower total corticosterone from day 19 through 22. Corticosteroid-binding globulin binding capacity was also significantly decreased in these fetuses for the last 4 days of gestation. Similar differences were noted in maternal samples. However, no significant differences in unbound, biologically active, corticosterone were seen when diabetic and control groups were compared. Thus, delayed fetal lung maturation observed in fetuses of streptozotocin-diabetic rats is associated with a decrease in total circulating corticosteroid levels late in gestation. However, since unbound corticosteroid levels were similar in fetuses of control and diabetic animals, it is likely that other mechanisms may be responsible for the observed delay in lung development in fetuses of diabetic pregnancies. (*Pediatr Res* 20: 155–160, 1986)**

**Abbreviations**

**CBG, corticosteroid-binding globulin**

Infants of diabetic mothers have a higher incidence of the respiratory distress syndrome than do infants of uncomplicated pregnancies (1). A perturbation or delay in the normal process of pulmonary maturation has also been demonstrated in a number of animal models of the diabetic gestation (2–6). However, at present, the precise mechanism responsible for this developmental delay is not known.

Endogenous glucocorticoids appear to have a physiologic role in the control of lung differentiation in the normally developing fetus (reviewed in Reference 7). It is well known that exogenous glucocorticoid administration can accelerate fetal lung maturation (reviewed in Reference 8). Previous studies of adrenal function and glucocorticoid levels in fetuses of diabetic pregnancies have yielded conflicting results. Early investigations of human diabetic pregnancies found either no change (9, 10) or increases (11, 12) in fetal or neonatal adrenal function and steroid levels in infants of diabetic pregnancies. In contrast, however, there is decreased amniotic fluid cortisol in human diabetic pregnancies (13, 14). Furthermore, recent studies with alloxan-diabetic rabbit (15) and streptozotocin-diabetic rat (16) have demonstrated decreased total glucocorticoid concentration in fetal plasma. However, none of these studies has measured the unbound, biologically active, steroid fraction in maternal and fetal plasma.

The present study was therefore designed to measure unbound and total corticosteroid levels in streptozotocin-diabetic rats and their fetuses, in order to investigate whether the delay in fetal lung maturation previously noted in this model (2, 3) can be accounted for by changes in circulating corticosteroid levels. CBG binding capacity was also assayed, since differences in binding capacity could affect the ratio of bound to unbound steroid.

## MATERIALS AND METHODS

*Animal model.* Diabetes was induced in nonpregnant female Sprague-Dawley rats (Charles River Breeding Laboratories, Boston, MA) by intravenous injection of streptozotocin (40 mg/kg) as previously described (2). The intravenous injection of this dose of streptozotocin reliably resulted in manifest diabetes, with a mean blood sugar of 498 ± 11 (range 300–600 mg/100 ml) *versus* a mean of 104 ± 2 for control animals (2). Fetuses were also hyperglycemic, with mean plasma glucose levels of 355 ± 10 *versus* 51 ± 4 for controls; in this system, however, fetuses were not hyperinsulinemic (mean plasma insulin = 75 ± 8 $\mu$ units/ml *versus* 83 ± 9 for controls) (2), in keeping with observations by other investigators (17–19). After 5 days [to negate any possible direct effect of streptozotocin, which is cleared from the circulation in about 6 h (20)] rats were bred with normal males until successful mating occurred. Pregnant animals were then caged individually until time of decapitation. A 16:8 h light:dark cycle was in effect. Handling was kept to a minimum. All animals were killed between 0900 and 1100 h to minimize possible effects of diurnal variation on steroid levels. Animals were stunned with a sharp blow to the head and immediately killed by decapitation. Maternal and pooled fetal blood was obtained immediately after decapitation and then spun to sepa-

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rate the plasma, which was then frozen until analysis could be performed.

*Steroid assays.* Total corticosterone was measured by a modification of the competitive protein binding assay of Murphy (21), using human plasma as the source of CBG and dextran-coated charcoal to separate free from bound steroid. The interassay variability for the total corticosterone assay was 9%.

The proportion of total corticosterone which was unbound to CBG was determined according to the method of Martin *et al.* (22). A 100 μl plasma sample was incubated with a trace amount of $H^3$-corticosterone and allowed to equilibrate at 37° C for 30 min, after which a 25 μl aliquot is taken for determination of total radioactivity; the remainder is placed on ice for 30 min, after which non-CBG-bound steroid is removed by treatment with 25 μl of dextran-coated charcoal solution (3.75 g of activated charcoal and 0.375 g of dextran T500 in a 50 mM phosphate solution, pH 7.4) for 10 min on ice. The dextran-charcoal-treated plasma is then centrifuged at 3000 × *g* for 10 min at 4° C after which a 50-μl aliquot is removed and radioactivity measured by scintillation counting to determine CBG-bound steroid levels. Non-CBG-bound corticosterone concentration is then calculated by multiplying the total counts − CBG-bound counts/total counts by the previously determined total corticosterone concentration. Interassay variability was 9%.

CBG-binding capacity was determined by the method of Martin *et al.* (22). Briefly, endogenous steroids are removed by incubating with dextran-coated charcoal and warming to 37° C for 30 min. Plasma is then diluted 1:100 (v:v) with 50 mM phosphate buffer. Two hundred μl of the diluted plasma containing $1 \times 10^{-7}$ M $H^3$-corticosterone is then incubated for 90 min on ice to determine total binding capacity. A similar incubation using $1 \times 10^{-7}$ M of $H^3$-corticosterone and $1 \times 10^{-5}$ M of nonradioactive corticosterone as a competitor is performed to determine nonspecific binding. Dextran-coated charcoal is then added, the samples centrifuged, and the radioactivity of the supernatants determined and compared to the radioactivity obtained prior to the addition of the dextran-coated charcoal. The total binding minus the nonspecific binding yields the CBG-binding capacity in ng/ml. Interassay variability was 14%.

One hundred eighty gestations of varying length were studied (105 control and 75 diabetic). Each day of gestation was studied independently, since steroid determination required termination of pregnancy. Thus, two-tailed Student's *t* test for independent variables was used to compare diabetic and control groups at the different gestational ages.

$H^3$-corticosterone was purchased from New England Nuclear (Boston, MA). Streptozotocin was received courtesy of Upjohn Company (Kalamazoo, MI). All other chemicals were obtained from Sigma Chemical Corp. (St. Louis, MO).

## RESULTS

Results for total and unbound corticosteroids and CBG-binding capacity in fetal plasma for the final 5 days of gestation are shown in Figure 1*a–c*. In control fetuses, total corticosterone concentration reached a peak on day 20 of gestation, and then declined progressively to term (Fig. 1*a*). The unbound corticosteroid, which accounted for only 5–10% of the total, increased approximately 3-fold after day 18, and maintained a level of 20–25 ng/ml from day 19 through term (Fig. 1*b*). CBG-binding capacity peaked on day 19 and then decreased steadily until term (Fig. 1*c*).

The fetuses of the diabetic pregnancies had significantly lower total corticosterone concentration when compared to controls on days 19, 21, and 22 (Fig. 1*a*). The overall shape of the developmental profile, with a peak at day 20, followed by decreasing corticosterone concentration through term, was the same for both groups of fetuses.

No significant differences in unbound corticosterone concentration between the diabetic and control groups were noted between days 18 and 22, although day 19 and 20 values tended to be lower (Fig. 1*b*). Both groups had significantly lower unbound corticosterone levels on day 18 than later in gestation. There was a greater than 2-fold increase in free:bound ratio over the final days of gestation in both diabetic and control groups.

Fetal CBG binding capacity was significantly lower in the experimental group on all days studied (Fig. 1*c*). Again, the shape of the developmental profile for CBG was the same in both groups, with a rise followed by a decreasing concentration until term; however, the peak in the diabetic group was on day 20 as opposed to day 19 for the control animals.

Data for maternal samples for the final 9 days of gestation are given in Figure 2*a–c*. Unlike control fetuses, which showed marked gestational changes in all three parameters, there were no consistent day-to-day changes in maternal control sera, with the possible exception of day 14 sera which had somewhat higher CBG capacity and lower unbound steroid than later in gestation. Diabetic mothers had significantly lower total corticosterone concentration when compared to control animals for the final 3 days of gestation, but not prior to that point in time (Fig. 2*a*). No significant differences in non-CBG-bound corticosterone were noted at any time in gestation between the two groups (Fig. 2*b*). However, CBG binding capacity in the diabetic mothers was decreased 2- to 3-fold on all days studied (Fig. 2*c*).

## DISCUSSION

Endogenous fetal glucocorticoids are thought to play a role in the regulation of fetal pulmonary maturation (7). There is a developmental increase in fetal plasma corticosteroid levels that correlates with increasing lung maturation in lambs (23) and rabbits (24). Umbilical cord blood cortisol levels (25) and amniotic fluid cortisol (26–28) have been found to correlate with indices of lung maturation. Decreased amniotic fluid and cord blood cortisol levels (28, 29) have been reported in neonates with respiratory distress syndrome.

Although there is evidence that experimentally induced diabetes can effect the morphology and function of the adrenal cortex (30–32) there have been few studies on the glucocorticoid status of the newborn infant (9–11) or fetus (12, 13, 15) of the diabetic pregnancy. In the human diabetic pregnancy, Gewolb *et al.* (13) demonstrated decreased unconjugated cortisol in amniotic fluid in diabetic gestations of greater than 30 wk when compared to age-matched uncomplicated pregnancies. Pschera *et al.* (14) also found lower amniotic fluid cortisol in diabetics between 31 and 40 wk of gestation, although differences did not reach significant levels. Guleff and Beck (15), in the alloxan-diabetic rabbit model, found decreased fetal plasma cortisol concentration and decreased *in vitro* fetal adrenal cortisol and corticosterone production in 28-day-old rabbit fetuses. No changes in fetal corticosterone concentration or in maternal levels of either steroid were noted. Mulay and Solomon (16) also reported decreased total maternal and fetal corticosterone levels in streptozotocin-diabetic rats between days 19 and 22 of gestation. The difference in fetal levels persisted for up to 6 h postpartum, but by 12–24 h after birth there were no significant differences between newborn rats born to diabetic and control mothers.

In the present study, the total plasma corticosterone in the fetus of the streptozotocin-diabetic rat was significantly decreased when compared to control values during the final days of gestation, consistent with the results of recent animal studies (15, 16). This decrease in total plasma corticoids was accompanied by a similar striking reduction in fetal plasma CBG-binding capacity in the experimental group. However, there were no significant differences from control values for unbound plasma corticosterone.

Our data on fetuses from control rat pregnancies are consistent

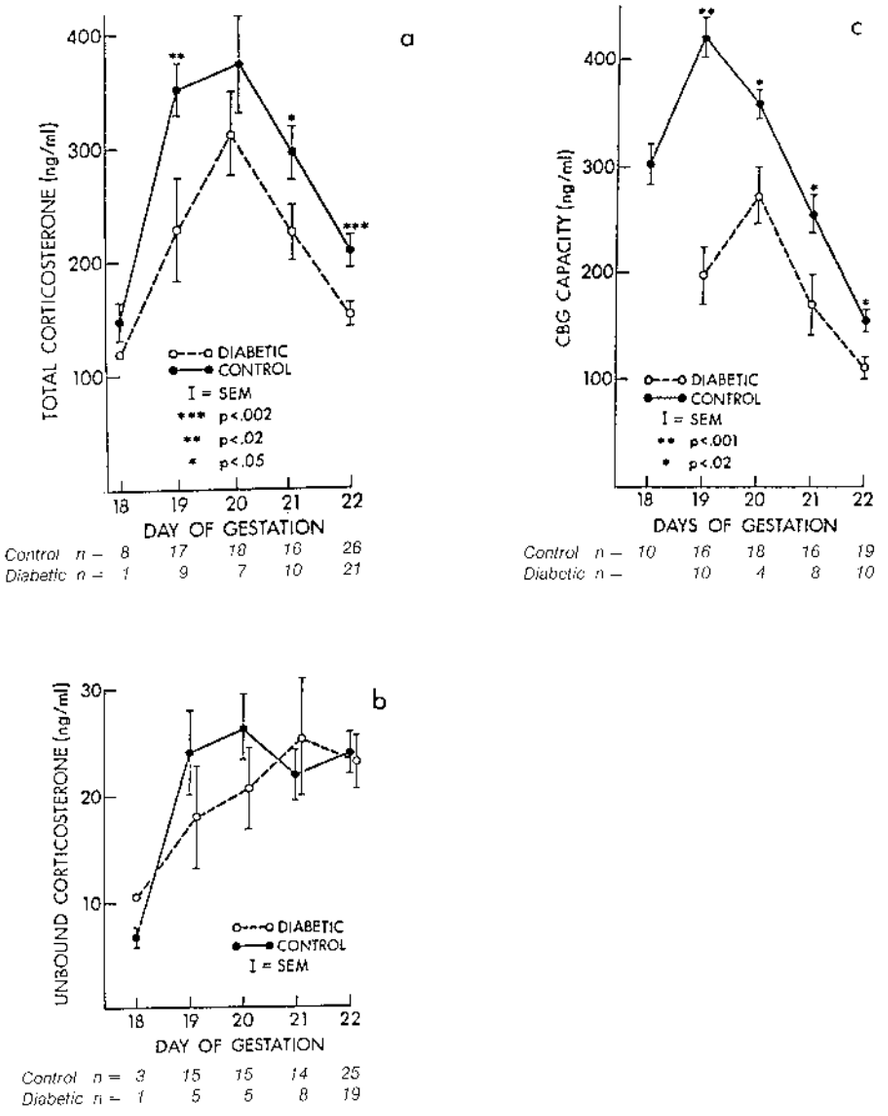


Fig. 1. *a*, total plasma corticosterone concentration in fetuses of control and diabetic gestations. *b*, unbound plasma corticosterone in fetuses of control and diabetic gestations. *c*, CBG-binding capacity in plasma from fetuses of control and diabetic gestations. Each *point* represents the mean ± SEM of a series of experiments terminated on the indicated day of gestation. *n* = the number of experiments studied for that day of gestation. Blood from four to eight fetuses from each pregnancy (depending on gestational age) was pooled; thus each pooled litter was considered a single experiment. All results are expressed in ng/ml. A single two-tailed Student's *t* test for independent variables was used to compare control and experimental conditions for each day of gestation.

with and the values similar to the results obtained by previous investigators studying normal rat gestation, who describe decreasing total corticosteroid concentration (16, 22, 33–35), CBG-binding capacity (22, 36), and increasing free fraction (22, 35) late in gestation. Martin *et al.* (22) reported a decrease in total fetal corticosteroid from a peak of 449 ng/ml 3 days prior to parturition to 77 ng/ml at birth, accompanied by a decrease in CBG from a peak of approximately 500 ng/ml 4 days prior to birth to about 100 ng/ml at term. Unbound steroid levels rose during this period in normal fetuses from approximately 15 to about 60 ng/ml (22). Mulay and Solomon (16) also described a decrease in fetal rat corticosterone concentration from approximately 1.1 mM/liter on day 19 to about 0.6 mM/liter at term. They did not measure CBG or the non-CBG-bound fraction. Cohen and Guillon (35) recently measured fetal corticosterone late in gestation; total corticosterone decreased from a peak of approximately 275 to about 125 ng/ml at term, while unbound corticosterone, measured by equilibrium dialysis, rose from 1 to 10 ng/ml at term.

Martin *et al.* (22) and others (36, 37) also found maternal levels of corticosterone to be relatively unchanged late in gestation in the rat with values ranging from 400–600 ng/ml, a level consistent with our data. Mulay and Solomon (16) and Dupuoy *et al.* (34) noted a rise in maternal corticosterone levels 3–4 days prior to term, but after that time they found that maternal corticosterone levels remained the same. Relatively constant maternal CBG levels were also found by Martin *et al.* (22) although their absolute values (200–400 ng/ml) are lower than our data for maternal CBG and much lower than their maternal total corticosterone values. In contrast, Van Baelen *et al.* (38) noted a slight decrease in maternal CBG levels late in gestation. Thus, although corticosterone crosses the rat placenta in both directions (34), the marked developmental changes in the fetal plasma, contrasted with relatively unchanging maternal param-

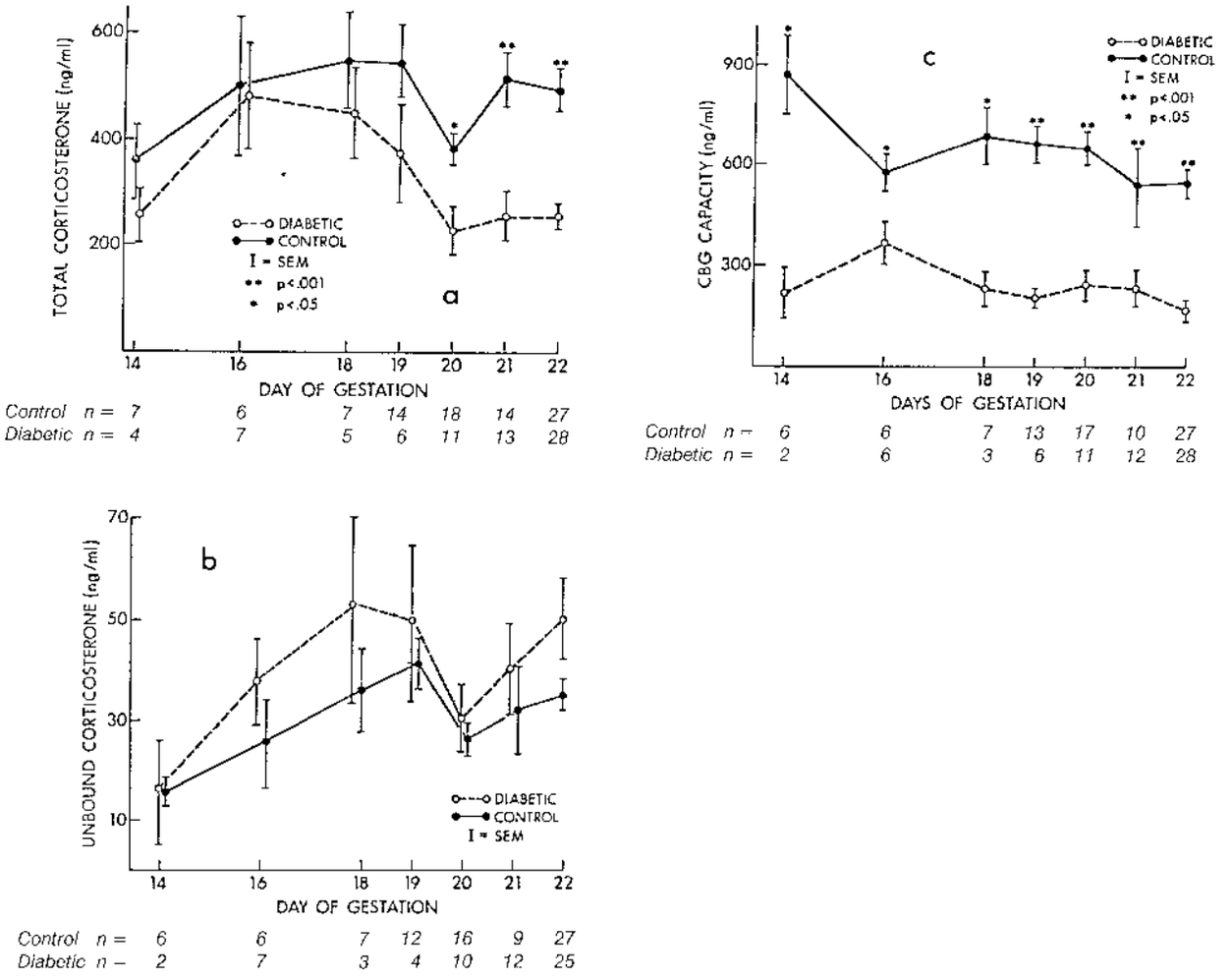


Fig. 2. *a*, total plasma corticosterone concentration late in pregnancy in control and diabetic rats. *b*, unbound plasma corticosterone concentration late in pregnancy in control and diabetic rats. *c*, CBG-binding capacity in plasma of control and diabetic rats late in pregnancy. Each *point* represents the mean ± SEM of a series of experiments terminated on day indicated. *n* = the number of pregnancies studied for each day. All results are expressed as ng/ml. Single two-tailed Student's *t* test for independent variables was used to compare means.

eters, and the difference between absolute maternal and fetal steroid levels suggest that the fetus has some independence in its ability to regulate its internal steroid milieu.

There are significant interspecies differences in the ontogeny of fetal steroid and steroid binding capacity during development. In the fetal sheep, corticoids rise progressively during gestation with an accelerated increase after 130 days of gestation; unbound steroid levels also increase late in gestation (39). In the fetal pig, total corticosteroid concentration increases 2- to 3-fold late in gestation, while maternal levels do not change significantly (40). In the fetal rabbit, total cortisol rises significantly late in gestation, followed by a 3-fold rise in unbound steroid levels (15, 24), although corticosterone levels do not change significantly (15). In the baboon fetus, cortisol concentration rises 4-fold (from 4 to 15 μg/dl) late in gestation, coincident with a decrease in CBG-binding-capacity from approximately 60 to 20 μg/dl at term (41). Similar increases in total fetal cortisol levels late in gestation and a higher percentage of unbound cortisol (approximately 25 *versus* 8% in adults) have been documented in human pregnancy (42, 43). Despite these interspecies variations, all appear to be characterized by increasing concentration of unbound steroids as term approaches.

The developmental profile of CBG also differs according to the species studied. CBG-binding capacity increases late in gestation in fetal sheep (39, 44) and in man (45–47) and parallels increased adrenocortical production and increased unbound steroid levels. In contrast, in the fetal baboon (41), rhesus monkey (48), rat (22, 35), and mouse (49), CBG-binding capacity decreases as term approaches, leading to the speculation that in these species, the increased unbound steroid concentrations seen late in gestation may be related to decreased CBG-binding capacity.

We have previously demonstrated a delay in fetal lung maturation by day 21 of the diabetic rat gestation. There was a decrease in whole lung phosphatidylcholine and disaturated phosphatidylcholine concentration in the diabetic group. This was accompanied by concommitant morphologic changes in the fetal lungs consistent with maturational delay (3).

The diabetic rat model used in this study differs from the human situation in a number of important parameters, most notably the lack of consistent fetal macrosomia and fetal hyperinsulinemia; thus, observations on the fetus of the diabetic rat are not necessarily applicable to the human diabetic pregnancy. Moreover, as noted above, the fetal developmental profile of glucocorticoid and CBG-binding capacity appears to be different in the rat fetus, where total corticosteroids and CBG decrease late in gestation, whereas these parameters increase in the 3rd trimester human fetus. Nevertheless, the finding of significantly lower total corticosteroid concentration in fetal plasma late in gestation in the fetus of the diabetic rat (and rabbit) raises the

possibility that the delay in fetal lung maturation seen in the diabetic pregnancy may be in part influenced by an abnormal steroid milieu. However, since no significant differences in the unbound steroid levels were noted between the diabetic and control groups in our study, the contribution of steroids to the process is less clear.

Binding of glucocorticoids to specific receptors in the lungs appear to be the mechanism whereby steroids exert their effect on development. Mulay and Solomon (16) noted a small increase in the cytoplasmic glucocorticoid receptor concentration in lungs of fetuses born to streptozotocin-diabetic rats. They suggested that this increased receptor concentration may be a compensatory mechanism to overcome the effects of decreased corticosterone concentration in these fetuses. In contrast, Boutwell and Goldman (50) found no difference in cytosolic steroid receptor concentration in streptozotocin-diabetic rat fetuses 1 day prior to term, but did observe decreased nuclear uptake of steroids in the experimental group. More work is needed to clarify the role of lung steroid receptors on lung development in fetuses of diabetic mothers.

The decreased CBG-binding capacity in both maternal and fetal plasma in diabetes may be related to decreased production in the liver or to increased trans-capillary protein loss (51), and thus may not be a specific effect on CBG; this point needs further investigation. The decrease in CBG-binding capacity observed in diabetes may have a compensatory function in the face of decreased adrenocortical production rate, by keeping the amount of free circulating steroid relatively constantly. Similarly, the fact that in normal rat gestation CBG-binding capacity declines parallel to and perhaps just prior to the fall in total corticosterone (Fig. 1*a* and *c*) has led to the speculation that fetal CBG may play a role in controlling maturational processes in the fetal rat by regulating the amount of unbound steroid able to interact with specific organ steroid receptors (7).

At present, the mechanism whereby the diabetic state leads to perturbed adrenocortical functioning is not clear. A direct effect of streptozotocin is unlikely since the majority of a dose of streptozotocin has been shown to be cleared from the rat circulation by 6 h (20), and mating was not begun in the present series of experiments until at least 5 days had elapsed (and many rats were not successfully impregnated for a number of weeks after injection). It is also unlikely that impairment of glucocorticoid production in the fetus of the streptozotocin-diabetic rat is the result of a direct insulin effect, since these fetuses are not hyperinsulinemic (2). Hyperglycemia may affect the adrenal function, but experimental data are conflicting. Hart *et al.* (52) noted that consumption of concentrated sugar solutions led to elevations in plasma corticosterone in rats; however, other studies (53) found a decrease in steroid levels. Further work is needed to clarify the reason(s) for the impaired adrenal function observed in some species with diabetes.

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# Erratum

It has come to our attention that the blood lactate concentrations published in the article "Effects of Acidosis on Fetal and Maternal Blood Coagulation: A Fetal Lamb Model" by Kisker CT, Bohlken DP, Clarke WR Pediatr Res 19:78–82, 1985, were in error due to a defect in the kit used for measuring the levels. Additional samples were available and the levels in the animals were remeasured.

**Although there is no change in the statistical outcome of the results,** line 8 on page 79 should read "an increase in the blood lactate level from 17–177 mg/dl." In Table 1 lactate levels should read as follows:

Table 1. *Results of in vivo exposure to lactic acid (mean ± SD)*

| | Fetus | | | | Ewe | | | |
|---|---|---|---|---|---|---|---|---|
| | Acidotic ($n = 10$) | | Control ($n = 8$) | | Acidotic ($n = 10$) | | Control ($n = 8$) | |
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Lactate (mg/dl) | 16 (±11) | 177 (±37) | 27 (±27) | 36 (±32) | 7.2 (±3.6) | 4.1 (+1.5) | 6.0 (±1.7) | 5.3 (±4.0) |