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Maternally Administered Dexamethasone at 0.7 of Gestation Suppresses Maternal and Fetal Pituitary and Adrenal Responses to Hypoxemia in Sheep

MICHELLE A. KUTZLER, TURHAN COKSAYGAN, A. DAMON FERGUSON, STELLA E. VINCENT, AND PETER W. NATHANIELSZ

Department of Clinical Sciences [M.A.K.], Oregon State University, Corvallis, OR 97331, U.S.A.; Departments of Biomedical Sciences [T.C.], Microbiology & Immunology [A.D.F.], and Population Medicine & Diagnostic Services [S.E.V.], Cornell University, Ithaca, NY 14853, U.S.A.; and Department of Obstetrics and Gynecology [P.W.N.], New York University School of Medicine, New York, NY 10016, U.S.A.

ABSTRACT

Women who are at risk of preterm delivery are treated with antenatal steroids to facilitate fetal lung maturation. During this period, there is a potential for fetal or maternal hypoxemia to occur. Fetal responses to hypoxemia in sheep are well documented. However, less is known regarding maternal responses to hypoxemia. Therefore, we determined the effects of dexamethasone (DM) on maternal and fetal responses to hypoxemia in sheep. Ewes received four i.m. injections of DM or saline at 12-h intervals beginning at 103 d of gestation. Samples for ACTH, cortisol, and glucose were collected at 0900 h. At 105 d of gestation, hypoxemia was induced for 1 h by maternal nitrogen gas inhalation. Samples for ACTH, cortisol, and glucose were collected at 15-min intervals before, during, and after the hypoxemia challenge. Fluorescent microspheres were administered to the mother and the fetus before and during hypoxemia to measure organ perfusion. DM suppressed basal fetal and maternal cortisol and ACTH concentrations but increased glucose levels. DM also increased fetal but not maternal blood pressure. In control subjects, hypoxemia elevated fetal and maternal cortisol and ACTH concentrations. These responses were obliterated by DM. Hypoxemia increased blood pressure in DM-exposed fetuses but not in control subjects. In addition, hypoxemia decreased fetal adrenal vascular resistance in saline but not DM fetuses or ewes from either treatment group. In summary, maternal administration of a low dose of DM at 0.7 of gestation suppresses maternal and fetal adrenal function and changes fetal responses to hypoxemic stress to resemble those observed later in gestation. **(*Pediatr Res* 55: 755–763, 2004)**

Abbreviations

BP, blood pressure
dGA, days of gestation
DM, dexamethasone
HR, heart rate
O_2 sat, arterial oxygen saturation of hemoglobin
Pao_2, arterial pressure of oxygen
$Paco_2$, arterial pressure of carbon dioxide

Administration of synthetic glucocorticoids, such as betamethasone and dexamethasone (DM), to accelerate fetal lung maturation has become a routine treatment for women who are at risk of preterm labor (1, 2). This treatment is designed to elevate fetal plasma glucocorticoid levels, mimicking the maturational effects that normally occur close to term in humans and other species produced by the endogenous prepartum increases in fetal plasma cortisol (3–6). Prophylactic antenatal glucocorticoid treatment has resulted in a significant decrease in preterm infant morbidity and mortality (1, 7–12).

Despite the clear benefits of antenatal maternal glucocorticoid therapy, unwanted effects on organ systems other than the lung have been identified in both clinical human and research animal studies. For instance, exogenous glucocorticoid use has been associated with reduced weight and head circumference in infants at birth (7, 13, 14). In addition to the effects on fetal growth, antenatal glucocorticoid treatment administered to fetal sheep in the last third of gestation increases fetal blood pressure (BP) (15–19). Repeated maternal betamethasone administration in sheep also suppresses neuroendocrine and adrenal responsiveness in the preterm newborn lamb (20, 21).

Responses to acute hypoxemia in fetal sheep >120 d of gestation (dGA) are well established (22–25). Acute fetal hypoxemia evokes orchestrated cardiovascular, metabolic, and

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Correspondence: Michelle Kutzler, DVM, PhD, DACT, Oregon State University, College of Veterinary Medicine, Department of Clinical Sciences, 158 Magruder Hall, Corvallis, OR 97331, U.S.A.; e-mail: michelle.kutzler@oregonstate.edu
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endocrine responses that aid in fetal survival during periods of reduced O_2 availability. However, relatively little is known about fetal responses to acute hypoxemia before 120 dGA. Cardiovascular responses of fetal sheep to hypoxemia before 100 dGA are different from those of fetal sheep at >100 dGA (26, 27). In addition, gestational changes in organ blood flow (28) and neurohormonal regulation (29) suggest that the responses to acute hypoxemia in fetuses <120 dGA would be different from those >120 dGA.

Studies investigating the effects of glucocorticoids on the capacity of the fetus (>120 dGA) to respond to hypoxemia have shown that treatment of fetal sheep either with cortisol administered i.v. for 5 h (30) or for 48 h (31) or with DM administered by an implant (700 μg) adjacent to the paraventricular nucleus (32) suppresses pituitary and adrenal responses to acute hypoxemia. However, the effect of maternal antenatal DM administration on the fetal responses to acute hypoxemia at <120 dGA is unknown. Similarly, there is no information on the effects of DM administration to the pregnant ewe on maternal endocrine and cardiovascular responses to acute hypoxemia.

We hypothesized that a single 48-h course of DM at 0.7 of gestation would suppress maternal and fetal adrenal responses and accelerate the normal cardiovascular responses to a 1-h episode of hypoxemia. We chose this gestational age because it corresponds to the stage of fetal development at which prophylactic therapy is given to women in premature labor. We focused our studies on the metabolic, neuroendocrine, and organ perfusion responses to DM.

METHODS

Care of animals. A total of 10 Rambouillet ewes (60–70 kg) carrying singleton fetuses of known gestational age were studied. Ewes were housed in individual metabolic cages and had free-access to pelleted feed and water. Ewes were maintained on a 14-h light/10-h dark cycle. All experimental procedures were approved by the Cornell University Institutional Animal Care and Use Committee, and the facilities were approved by the Association for Assessment and Accreditation of Laboratory Animal Care.

Surgical procedures. Surgery was performed at 96 ± 1 dGA (term 149 dGA). Ewes were premedicated with 1 mg of glycopyrrolate (Robinul-V (R), Fort Dodge Animal Health, Overland Park, KS, U.S.A.) i.m. and given 1 g of ampicillin (Polyflex, Ayerst Veterinary Laboratories, Guelph, Ontario, Canada) i.m. After administration of 1 g of ketamine (Ketaflo; Abbott Laboratories, North Chicago, IL, U.S.A.) i.m., anesthesia was induced with 4% isoflurane gas (Isoflo; Abbott Laboratories) administered with a face mask. Ewes were intubated, and anesthesia was maintained with 1.5–2.0% isoflurane and O_2 with a flow rate of 2–3 L/min *via* positive-pressure ventilation. The right side and ventral midline of the ewe's neck as well as her ventral abdomen from xiphoid to pubis were shaved and prepared aseptically for surgery.

Each ewe was instrumented with left ventricular, carotid, and femoral artery; jugular and femoral vein; and tracheal catheters. The left ventricular and carotid artery catheters both were placed within the right carotid artery. Exact placement of the ventricular catheter was confirmed using a pressure transducer (Disposable BP Transducer, model no. MLT 0670; PowerLab AD Instruments, Colorado Springs, CO, U.S.A.) and data acquisition software (WINDAQ, DATAQ Instruments). The femoral artery and vein catheters were advanced until their tips were in the descending aorta or inferior vena cava, respectively. All catheters were prefilled with heparinized saline (20 IU/mL).

The gravid uterus was exposed through a ventral midline abdominal incision. The fetal neck was exteriorized through a uterine incision, and a jugular vein and carotid artery catheter were placed. An additional catheter was secured to the skin of the fetal neck for monitoring intra-amniotic pressure. The fetus was returned to the uterus, and the uterine incision was closed. Next, a fetal hind limb was exteriorized through a second uterine incision. A catheter was inserted into the fetal descending aorta *via* the femoral artery, and another catheter was inserted into the fetal inferior vena cava *via* the pedal vein. The second uterine incision was closed, and all catheters were exteriorized through the flank of the ewe. Teflon-coated stainless steel wire electrodes were sewn into the myometrium to permit continuous monitoring of uterine electromyographic activity, and the abdominal incision was closed in layers.

Postoperative care. Ampicillin (500 mg, Amp-Equine; Pfizer Animal Health, Philadelphia, PA, U.S.A.) was administered postoperatively twice daily for 5 d to the ewe and the fetus *via* the jugular and amniotic catheters, respectively. The ewes also received 3 d of oral phenylbutazone (0.5–1.0 g, Phenylzone paste; Schering-Plough, Kenilworth, NJ, U.S.A.) daily for postoperative analgesia. Vascular catheters were maintained patent by a continuous infusion of heparinized saline (20 IU/mL) at 0.5 mL/h. Animals were allowed at least 4 d to recover from surgery before baseline measurements were taken.

Experimental procedures. Ewes received four i.m. injections of either 2 mg of DM (Azium, Schering; $n = 6$) or saline ($n = 4$) at 12-h intervals beginning at 103 dGA (~30 μg/kg DM, weight-adjusted dose). At 105 dGA and 47 h after the onset of treatment, fetal hypoxemia was induced by maternal nitrogen gas inhalation in both treatment groups as previously described (33) to reduce fetal arterial pressure of oxygen (Pa_{O_2}) by ~40% of baseline values. After 1 h, nitrogen gas delivery was discontinued and the ewe was allowed to breathe room air for an additional 15 min. Ewes were then killed by an overdose (15 mL) of pentobarbital sodium (Fatal Plus; Vortech Pharmaceuticals, Dearborn, MI, U.S.A.). The positioning of catheters was confirmed at necropsy.

Paired maternal and fetal carotid artery samples were taken daily during a period of minimal uterine electromyographic activity for the analysis of arterial blood gases and measurement of blood glucose and plasma hormone concentrations. Samples were taken at 0900 h on the day before the treatment began (T-1) and on the 2 d during treatment (T1 and T2), as well as 30 and 15 min before, during (15 and 45 min after the onset of hypoxemia), and 15 min after the period of hypoxemia. Plasma samples for hormone measurements were stored at −70°C until analyzed. Additional fetal carotid arterial blood

gas samples were taken at 5-min intervals until 20 min into the hypoxemia challenge to confirm that fetal Pao_2 was within the targeted range. The volume of fetal blood removed for each sample (5 mL) was replaced with an equal volume from an age-matched donor animal.

Blood gas measurements. Fetal and maternal Pao_2, arterial pressure of carbon dioxide ($Paco_2$), pH, and glucose were measured with a blood gas analyzer (ABL 500; Radiometer Medical A/S, Copenhagen, Denmark) with measurements corrected to core body temperature (39°C). Arterial oxygen saturation of Hb (O_2 sat) and Hb concentration were measured with a hemoximeter (OSM 2; Radiometer Medical A/S).

Hemodynamic measurements. Fetal and maternal aortic BP, inferior vena cava pressure, heart rate (HR), and amniotic pressure were recorded continuously with pressure transducers (Disposable BP Transducer, model no. MLT 0670; PowerLab AD Instruments). Maternal and fetal mean arterial blood pressure were corrected for central venous pressure. In addition, fetal mean arterial BP was corrected for intra-amniotic pressure. Pressure, HR, and electromyographic signals were digitized with a data acquisition program (WinDAQ, DATAQ Instruments, Akron, OH, U.S.A.).

Hormone analysis. Maternal and fetal plasma ACTH concentrations were measured using a solid-phase, two-site chemiluminescence enzyme immunometric assay (DPC Immulite assay; Diagnostic Products Co., Los Angeles, CA, U.S.A.) on an automated immunoassay analyzer (IMMULITE; Diagnostic Products Co.). In addition to ACTH 1-39, cross-reactivity was detected only with ACTH (18-39) at 13 and 15% for 500 and 5000 pg/mL added. The sensitivity of the assay (defined as the concentration 2 SD above zero) was 9 pg/mL plasma. For samples measuring 20 and 200 pg/mL, the intra-assay coefficients of variation were 4.75 and 3.54%, respectively. For samples measuring 50 and 150 pg/mL, the interassay coefficients of variation were 12.01 and 16.46%, respectively. Values are expressed as pg/mL.

Maternal and fetal plasma cortisol concentrations were measured using a modified (standard curve from 2.5–500 ng/mL, sample volume = 50 μL) DPC Coat-A-Count RIA kit (Diagnostic Products Co.). The cross-reactivity with prednisone and prednisolone was 7.6 and 2.3%, respectively. The cross-reactivity of 11-deoxycortisol was 11.4%. Cross-reactivities to other steroids were <1%. The sensitivity of the assay (defined by 90% bound/free) was 2 ng/mL plasma. For plasma pools measuring 28 and 144 ng/mL, the interassay coefficients of variation were 8.66 and 8.03% and the intra-assay coefficients of variation were 4.14 and 3.2%, respectively. Values are expressed as ng/mL.

Measurement of regional organ flows. Ten minutes before the induction of hypoxemia, 4 million fluorescent microspheres (15 μm; Molecular Probes, Eugene, OR, U.S.A.) were injected into the maternal left ventricular catheter as well as the fetal femoral and jugular vein catheters (2 million microspheres per fetal catheter) as previously described (34). Reference blood samples for measuring blood flow were collected simultaneously from the maternal femoral artery and fetal femoral and carotid arteries at a constant rate of 3.88 mL/min. Fluorescent microspheres were again administered 10 min before the end of hypoxemia. For each microsphere injection, a fluorescent color with a distinct excitation and emission wavelength was used. This method for measuring blood flow was previously validated in our laboratory (34).

Fetal and maternal tissues were collected at necropsy for microsphere retrieval. From the fetus, the whole adrenal glands (adrenal) and a 1- to 2-g biopsy from left ventricle (cardiac), left frontal cortex (cortical), left femoral muscle, and left renal cortex (renal) were individually weighed and placed in a glass test tube. From the ewe, a 1- to 2-g biopsy taken from the left adrenal cortex, left adrenal medulla, left femoral muscle, and left renal cortex (renal) was sampled. Briefly, tissues were digested with potassium hydroxide, and the liberated fluorescent microspheres were separated by filtration from the tissue hydrolysate. The fluorescent dyes from the microspheres were then extracted with a solvent (2-ethoxyethyl acetate; Cellusolve, Aldrich Chemical Co. Inc., Milwaukee, WI, U.S.A.). The fluorescence of the dye-containing solution was quantified in a fluorometer (Fluoromax-II Instruments S. A. Inc., Edison, NJ, U.S.A.).

Data analysis. During the baseline and treatment days, mean maternal and fetal arterial BP and HR were calculated at hourly intervals for 72 h. During the hypoxemia challenge, mean maternal and fetal arterial BP and HR were calculated at 15-min intervals from 30 min before the onset of hypoxemia until 15 min after the end of hypoxemia. Blood gas, glucose, ACTH, cortisol, and BP data collected at 30 and 15 min before onset of hypoxemia, 15 and 45 min after onset of hypoxemia, and 15 min after the end of hypoxemia were averaged and reported as Pre-HX, HX, and Post-HX, respectively. Incremental increases in glucose concentrations were determined with respect to prehypoxemia baseline values for each individual and then calculating the mean for the group. Fetal organ perfusion pressure was calculated as the difference between the mean arterial BP and the venous pressure after correction for intra-amniotic pressure. Maternal organ perfusion pressure was calculated as the difference between the mean arterial BP and the venous pressure. Basal (Pre-HX) and hypoxemia (HX) organ blood flow (ml $\cdot$ min $^{-1}$ $\cdot$100 g tissue^{-1}) was determined 10 min before and 50 min after the onset of hypoxemia, respectively. Maternal and fetal organ vascular resistances (mm Hg $\cdot$ ml^{-1} $\cdot$min$\cdot$ 100 g tissue^{-1}) were calculated as the quotient of organ perfusion pressure divided by mean organ blood flow. Values are expressed as mean $\pm$ SEM unless otherwise stated. Changes in variables within and between treatment groups were assessed using a one-way ANOVA with Tukey's *post hoc* test. Statistical significance was accepted at $p < 0.05$.

RESULTS

Arterial blood gas, acid-base, and metabolite status. In the control animals, all fetal and maternal blood gas parameters and plasma glucose concentrations were within the normal range and did not change during the treatment period (Table 1). DM treatment had no effect on daily blood gas parameters in the fetuses and ewes. However, both fetal and maternal glucose

Table 1. *Effect of DM treatment on blood gas and glucose status*

	Saline					
	Fetal			Maternal		
Sample	T-1	T1	T2	T-1	T1	T2
pH	7.34 ± 0.012	7.33 ± 0.010	7.34 ± 0.006	7.45 ± 0.015	7.46 ± 0.016	7.51 ± 0.030
Pa_{O_2} (mm Hg)	24.7 ± 1.46	25.6 ± 0.36	23.2 ± 1.46	122.2 ± 7.47	123.8 ± 7.54	111.8 ± 8.13
Pa_{CO_2} (mm Hg)	49.6 ± 1.61	52.3 ± 1.08	51.6 ± 1.48	37.3 ± 1.59	37.8 ± 1.06	39.6 ± 1.67
O_2 sat (%)	58.2 ± 5.66	63.7 ± 6.42	62.3 ± 3.72	94.3 ± 2.85	97.7 ± 0.85	94.5 ± 0.81
Hb (mg/dL)	7.9 ± 0.20	8.1 ± 0.33	8.5 ± 0.32	8.7 ± 0.09	8.9 ± 0.28	9.3 ± 0.82
Hct (%)	28.5 ± 3.54	31.0 ± 2.12	32.7 ± 0.92	26.5 ± 2.05	30.0 ± 1.41	29.5 ± 3.05
Glucose (mmol/L)	1.1 ± 0.20	1.1 ± 0.14	1.0 ± 0.14	3.5 ± 0.33	3.4 ± 0.28	3.7 ± 0.24
	DM					
	Fetal			Maternal		
Sample	T-1	T1	T2	T-1	T1	T2
pH	7.34 ± 0.009	7.34 ± 0.005	7.33 ± 0.016	7.47 ± 0.037	7.47 ± 0.010	7.52 ± 0.011
Pa_{O_2} (mm Hg)	23.8 ± 1.54	25.5 ± 1.28	28.1 ± 2.71	126.0 ± 6.26	113.9 ± 3.45	123.6 ± 5.43
Pa_{CO_2} (mm Hg)	51.8 ± 2.91	48.1 ± 2.28	48.2 ± 2.22	38.8 ± 1.10	38.1 ± 2.17	36.9 ± 2.83
O_2 sat (%)	61.3 ± 3.94	68.8 ± 3.42	68.2 ± 2.53	97.8 ± 0.66	90.0 ± 5.05	95.2 ± 1.06
Hb (mg/dL)	7.9 ± 0.56	8.9 ± 0.53	8.7 ± 0.76	10.1 ± 0.52	9.5 ± 0.44	9.1 ± 0.28
Hct (%)	30.8 ± 2.03	34.2 ± 2.64	33.4 ± 3.55	28.7 ± 0.91	30.8 ± 1.88	30.2 ± 1.73
Glucose (mmol/L)	0.9 ± 0.08	1.6 ± 0.19*	1.5 ± 0.10*	3.3 ± 0.14	4.5 ± 0.31*	4.4 ± 0.20*

Hct, hematocrit.

Values are given for baseline (T-1), after the first treatment day (T1), and after the second treatment day (T2) after maternal administration of saline ($n = 4$) or DM ($n = 6$) for 48 h beginning at 09.0 h on 103 dGA. Mean ± SEM.

* $p < 0.05$ compared with baseline levels and saline-treated group.

concentrations were increased during the 48-h treatment period compared with baseline levels and the saline-treated groups.

Fetal blood gas parameters and glucose concentrations during the hypoxemia protocol are shown in Table 2. Before the onset of the hypoxemia challenge, values for fetal pH, Pa_{O_2}, Pa_{CO_2}, O_2 sat, Hb concentration, and hematocrit were not different between saline-infused and DM-treated animals. During hypoxemia, the decreases in fetal Pa_{O_2} and O_2 sat were similar in both groups. However, during hypoxemia, DM-treated fetal glucose concentrations remained greater than in the saline-treated group.

In fetuses of saline-treated ewes, blood glucose concentrations were elevated during HX compared with Pre-HX values (Table 2). Despite elevated Pre-HX blood glucose concentrations in DM-treated fetuses, hypoxemia further increased glucose levels compared with values from Pre-HX and saline-treated fetuses. At Post-HX, all blood gas parameters returned to Pre-HX levels in both treatment groups except for fetal blood glucose concentrations, which remained elevated Post-HX in the DM-treated group compared with Pre-HX and saline-treated values. The increment in fetal glucose concentration calculated with respect to Pre-HX values was decreased in the DM-treated group compared with the saline group during HX but increased at Post-HX.

Values for maternal carotid arterial blood gas parameters and glucose concentrations during the hypoxemia protocol are shown in Table 2. These variables were similar in the saline-treated and DM-treated ewes at Pre-HX. Maternal carotid Pa_{O_2} and O_2 sat fell rapidly to similar values in the saline-treated and DM-treated ewes during the hypoxemia challenge. Other blood gas parameters remained at Pre-HX values during the hypoxemia challenge and were not different between treatment groups. In saline-treated and DM-treated ewes, blood glucose concentrations remained unchanged during the hypoxemia challenge, with glucose levels from DM-treated ewes greater than in saline-treated ewes at all time points.

Hormone concentrations. Baseline plasma cortisol and ACTH concentrations were similar in both groups of fetuses and mothers (Fig. 1). During 48 h of DM treatment, fetal and maternal cortisol concentrations were decreased compared with baseline and saline-treated values. Similarly, ACTH concentrations from DM-treated fetuses were decreased during the 48-h treatment period compared with baseline and saline-treated values. However, ACTH concentrations from DM-treated mothers were not significantly decreased until the last 24 h during the treatment period compared with baseline and saline-treated levels.

In saline-treated fetuses and mothers, significant increases in plasma cortisol and ACTH concentrations occurred during hypoxemia when compared with Pre-HX levels (Fig. 2). In the saline-treated fetuses and mothers, plasma cortisol concentrations remained elevated Post-HX, whereas ACTH concentrations remained increased only in comparison with Pre-HX in the mothers. In contrast, no rise in plasma ACTH or cortisol concentrations occurred during acute hypoxemia in the DM-treated fetuses or mothers.

Maternal and fetal blood pressure and regional blood flows. DM administration elevated fetal BP after the first three injections without affecting maternal BP (Fig. 3). Acute hypoxemia did not increase maternal BP in either treatment group, but DM-treated fetal BP was increased (Table 2). The effects of DM treatment and hypoxemia on fetal organ blood flow and vascular resistance are summarized in Figure 4. During normoxia after a 48-h treatment

Table 2. *Effect of a hypoxemia challenge on blood gas status, glucose concentration, BP, and HR*

	Saline					
	Fetal			Maternal		
Sample	Pre-HX	HX	Post-HX	Pre-HX	HX	Post-HX
pH	7.34 ± 0.006	7.35 ± 0.013	7.34 ± 0.016	7.51 ± 0.031	7.50 ± 0.015	7.48 ± 0.010
Pao_2 (mm Hg)	23.2 ± 1.46	14.2 ± 1.08*	22.0 ± 1.17	111.8 ± 8.12	50.7 ± 4.72*	117.1 ± 5.47
$Paco_2$ (mm Hg)	51.6 ± 1.48	48.7 ± 1.52	50.1 ± 2.08	39.6 ± 1.67	34.8 ± 1.84	38.9 ± 1.95
O_2 sat (%)	62.3 ± 3.72	32.4 ± 5.66*	63.2 ± 1.66	94.5 ± 0.81	55.5 ± 12.00*	95.2 ± 0.42
Hb (mg/dL)	8.5 ± 0.32	8.6 ± 0.81	8.5 ± 0.33	9.3 ± 0.82	10.1 ± 0.55	9.1 ± 0.45
Hct (%)	32.7 ± 0.92	29.6 ± 2.46	31.0 ± 1.80	29.5 ± 3.05	30.9 ± 2.23	29.5 ± 2.33
Glucose (mmol/L)	1.0 ± 0.14	1.6 ± 0.21*	1.0 ± 0.25	3.7 ± 0.24	3.6 ± 0.20	4.0 ± 0.24
IG (mmol/L)		0.56 ± 0.000	0.00 ± 0.000			
BP (mm Hg)	40.1 ± 2.53	40.3 ± 0.71	41.9 ± 0.40	90.5 ± 3.58	89.6 ± 4.37	86.4 ± 3.66
HR	187.3 ± 9.96	184.9 ± 6.07	186.3 ± 10.21	99.4 ± 10.28	100.2 ± 6.58	98.9 ± 4.66
	DM					
	Fetal			Maternal		
Sample	Pre-HX	HX	Post-HX	Pre-HX	HX	Post-HX
pH	7.33 ± 0.016	7.3 ± 0.047	7.31 ± 0.013	7.52 ± 0.011	7.53 ± 0.011	7.50 ± 0.011
Pao_2 (mm Hg)	28.1 ± 2.71	17.3 ± 1.84*	25.4 ± 0.91	123.6 ± 5.43	50.1 ± 5.36*	122.3 ± 3.41
$Paco_2$ (mm Hg)	49.9 ± 1.50	46.6 ± 1.98	46.7 ± 1.80	36.9 ± 2.83	31.9 ± 0.88	35.0 ± 2.29
O_2 sat (%)	68.2 ± 2.53	40.0 ± 3.53*	66.7 ± 2.03	95.2 ± 1.06	71.2 ± 7.71*	95.6 ± 0.72
Hb (mg/dL)	8.7 ± 0.76	7.7 ± 1.24	8.6 ± 0.41	9.1 ± 0.28	9.6 ± 0.45	9.5 ± 0.28
Hct (%)	33.4 ± 3.55	29.5 ± 2.19	29.7 ± 1.54	29.3 ± 1.62	29.8 ± 1.46	28.2 ± 2.17
Glucose (mmol/L)	1.5 ± 0.10	1.9 ± 0.08*†	2.1 ± 0.17*†	4.4 ± 0.20†	4.3 ± 0.14†	4.6 ± 0.08†
IG (mmol/L)		0.39 ± 0.000†	0.53 ± 0.000†			
BP (mm Hg)	44.1 ± 1.62	48.0 ± 2.75*†	48.9 ± 1.65*†	95.0 ± 9.02	97.9 ± 9.07	92.5 ± 7.89
HR	186.4 ± 10.28	183.6 ± 5.58	185.8 ± 11.81	94.6 ± 10.34	93.4 ± 14.88	97.7 ± 10.78

IG, incremental increase in glucose concentration.

Data collected at 30 and 15 min before onset of hypoxemia (Pre-HX), 15 and 45 min after onset of hypoxemia (HX), and 15 min after the end of the hypoxemia (Post-HX) were averaged from mothers and fetuses at 105 dGA that were treated with saline ($n = 4$) or DM ($n = 6$) for 48 h before hypoxemia. Mean ± SEM.

* $p < 0.05$ compared with Pre-HX.

† $p < 0.05$ compared with saline-treated controls.

period of DM, adrenal blood flow was reduced and adrenal vascular resistance was increased compared with saline-treated fetuses. Acute hypoxemia increased fetal adrenal blood flow in both treatment groups, but adrenal vascular resistance decreased only in saline-treated fetuses. In addition, cardiac blood flow increased in both treatment groups, in association with a decrease in cardiac vascular resistance during hypoxemia. Hypoxemia reduced fetal renal cortex blood flow in saline-treated animals but not in DM-treated

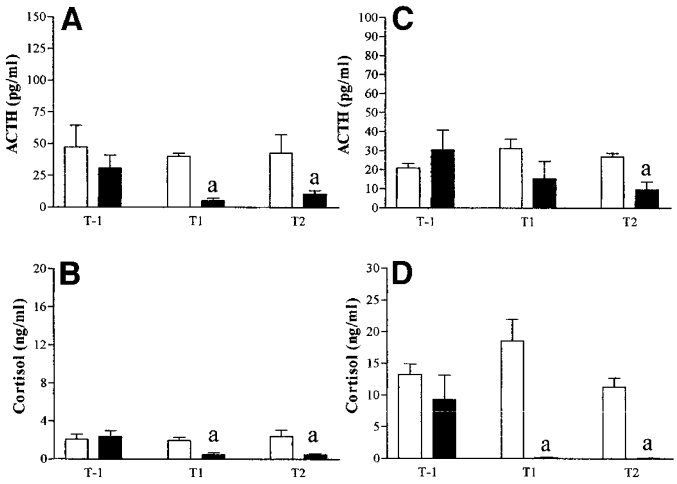

Figure 1. Fetal plasma ACTH (*A*) and cortisol (*B*) and maternal plasma ACTH (*C*) and cortisol (*D*) concentrations measured at baseline (T-1), after the first treatment day (T1) and after the second treatment day (T2) from pregnant ewes that were treated with saline (□; $n = 4$) or DM (■; $n = 6$) for 48 h beginning at 0900 h at 103 d of gestation. Mean ± SEM; $^a p < 0.05$ compared with baseline and saline-treated group.

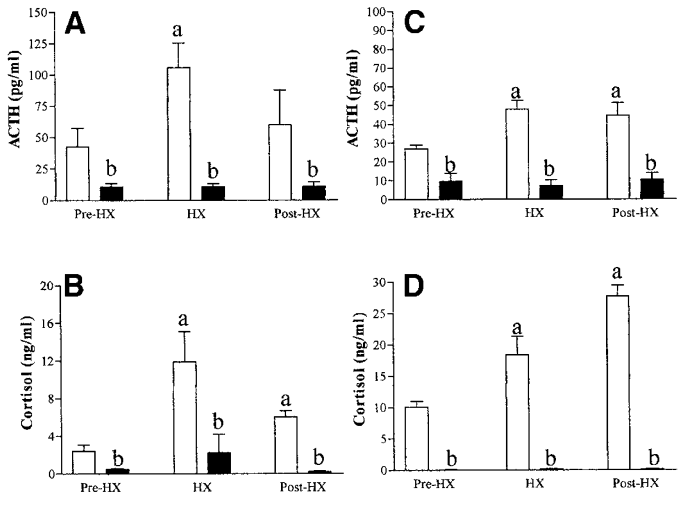

Figure 2. Fetal plasma ACTH (*A*) and cortisol (*B*) and maternal plasma ACTH (*C*) and cortisol (*D*) concentrations measured 15–30 min before (Pre-HX), during (HX), and 15 min after (Post-HX) a 1-h hypoxemia challenge (decrease in fetal Pao_2 by 40%) from pregnant ewes at 105 dGA that were treated with saline (□; $n = 4$) or DM (■; $n = 6$) for 48 h before the challenge. Mean ± SEM; $^a p < 0.05$ compared with Pre-HX, $^b p < 0.05$ compared with saline-treated group.

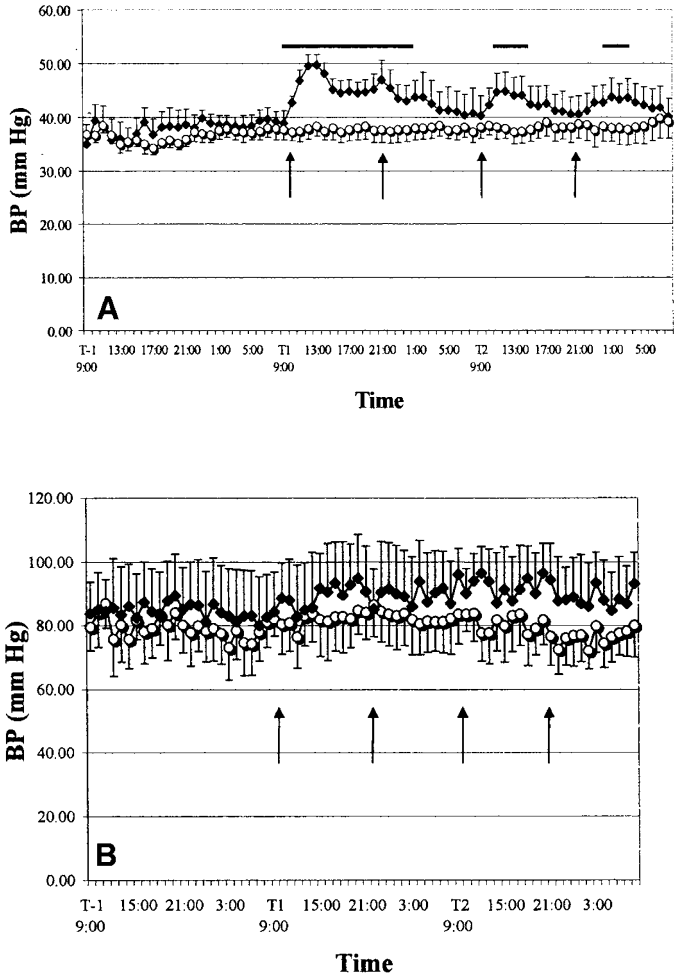

Figure 3. Fetal (*A*) and maternal (*B*) arterial BP measured from 102 dGA for a 24-h baseline period (T-1) and continued for 2 d during maternal saline (○) or DM (●; T1 and T2) treatment with arrows indicating the time of the injection. Mean ± SEM; bars indicate time points when BP was different from saline group ($p < 0.05$).

fetuses. This change was due to an increase in vascular resistance in the saline-treated group. Hypoxemia reduced femoral blood flow in saline-treated animals, whereas femoral vascular resistance was increased in both treatment groups with a greater increase after DM treatment. In addition, hypoxemia increased cerebral cortical blood flow in DM-treated fetuses but not in the saline group, although cortical vascular resistance did not change significantly.

The effects of hypoxemia on maternal organ blood flow are also summarized in Figure 4. There were no DM-induced changes in organ blood flow before hypoxemia, but femoral vascular resistance was higher in the DM-treated ewes. Acute hypoxemia decreased renal cortex and femoral muscle blood flow in saline-treated mothers but not in the DM-treated mothers. Femoral vascular resistance increased in both treatment groups during hypoxemia. Neither glucocorticoid treatment nor hypoxemia significantly changed maternal adrenal cortical or medullary blood flow in both the saline and DM-treated groups.

DISCUSSION

Effects of DM treatment and hypoxemia on blood gas status. Fetal blood gas values at 105 dGA presented here were similar to those reported in other studies in the last third of gestation (24, 25, 31, 35–37). DM treatment had no effect on fetal or maternal blood gas values. In addition, blood gas values from ewes at 105 dGA were similar to what has been reported in ewes in the later stages of pregnancy (31, 37). During hypoxemia, the fall in neither Pao_2 nor O_2 sat was influenced by DM treatment. Previous studies have reported that acute fetal hypoxemia results in changes in blood gas values, such as a decreased pH, increase in hematocrit, and increase or decrease in Hb concentration (26, 31, 36–39). In this study, we found no significant changes in fetal or maternal arterial pH, $Paco_2$, Hb concentration, or hematocrit during 1 h of reduced maternal inspired O_2. This finding is in agreement with previous studies in saline-infused (40) and cortisol-infused fetuses (30).

Effects of DM treatment and hypoxemia on glucose concentration. As reported in older fetuses (31, 41), DM treatment produced a profound hyperglycemic response in both fetuses and pregnant ewes at 103–104 dGA. Glucocorticoid administration increases hepatic glycogen content (42) and hepatic and renal gluconeogenic enzyme activities (43). Our observations therefore suggest a glucocorticoid-accelerated maturation of fetal glucose mobilization.

Acute hypoxemia increased fetal glucose concentrations, which remained higher in DM-treated fetuses compared with control fetuses during and after the hypoxemia challenge. In the only other study published on the effects of hypoxia on glucose concentrations at this stage of gestation, fetal hyperglycemia did not occur (44). However, our findings are in agreement with research in older fetuses (>124 dGA) that were either infused with DM for 48 h (31) or had endogenously elevated cortisol concentrations (36), in which hypoxia produced higher glucose concentrations compared with controls. Changes in fetal plasma glucose in response to acute hypoxia are probably the result of catecholamine responses (45). In saline-treated ewes, we found that acute hypoxemia did not increase maternal glucose concentrations. However, similar to the observations in the fetuses, DM-treated mothers had elevated glucose concentrations at all time points of the hypoxemia challenge compared with controls.

Effects of DM treatment and hypoxemia on ACTH and cortisol concentrations. Our finding that maternal DM treatment at 105 dGA significantly reduced fetal cortisol and ACTH levels differs from previous studies in which fetal DM infusion had little effect on basal plasma ACTH and cortisol concentrations in fetuses >120 dGA (22, 31, 46). These findings are in keeping with the concept that the sensitivity of the hypothalamic-pituitary-adrenal system to negative feedback is greater earlier in gestation and disappears, thereby allowing the endogenous rise in cortisol that usually occurs at ~125 dGA (6, 47). We also found that maternal DM treatment reduced maternal cortisol and ACTH levels. It took an additional 24 h of DM treatment to decrease maternal ACTH compared with fetal levels, suggesting increased fetal pituitary sensitivity to the

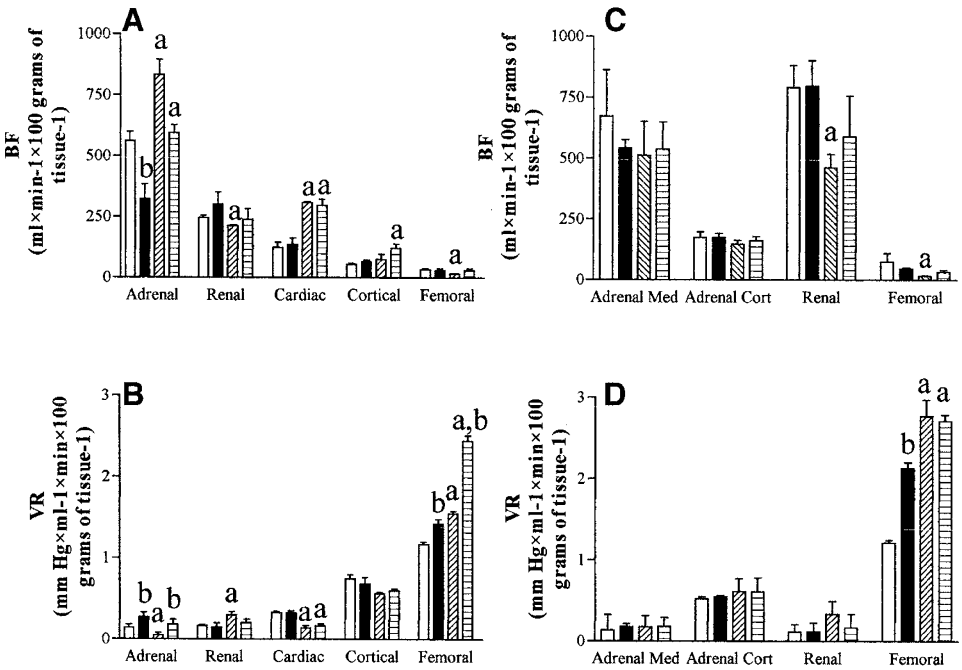

Figure 4. Fetal organ blood flow (BF; *A*) and vascular resistance (VR; *B*) and maternal organ BF (*C*) and VR (*D*) measured at 10 min before (Pre-HX) and 50 min into (HX) a hypoxemia challenge from fetuses at 105 dGA after maternal treatment with either DM or saline. Pre-HX saline (□; $n = 4$), Pre-HX DM (■; $n = 6$), HX saline (▨; $n = 4$), HX DM (▤; $n = 6$). Mean ± SEM; [a]$p < 0.05$ compared with Pre-HX; [b]$p < 0.05$ compared with saline-treated group.

negative feedback of glucocorticoids compared with the adult. The significant decrease in maternal cortisol in response to DM in the absence of a fall in maternal ACTH suggests an action of DM at the adrenal level in the adult.

The magnitude of fetal pituitary-adrenal responses to acute hypoxemia in the saline-treated group were greater than those reported previously for fetuses at later gestational ages (>120 dGA), although the baseline values were less (22, 25, 31, 37, 48, 49). In our study, we found that fetal cortisol concentrations at baseline were ~3 ng/mL and quadrupled to ~12 ng/mL during hypoxemia. Others have reported that between 127 and 130 dGA, baseline fetal cortisol concentrations range from ~12 to 20 ng/mL, which more than doubled to ~29–55 ng/mL during hypoxemia (25, 37). In the present study, fetal cortisol remained significantly elevated for 15 min after return to a normoxic condition, similar to a previous report in which umbilical cord compression increased endogenous fetal cortisol concentration (37). Saline-treated ewes responded to acute hypoxemia similarly to their fetuses, except that both cortisol and ACTH concentrations remained elevated 15 min after ending the hypoxemia challenge. One previous study in which maternal Pa_{O_2} was reduced to 57 mm Hg did not observe the maternal pituitary-adrenal response seen here to a maternal Pa_{O_2} of 50 mm Hg (24).

Effects of DM treatment and hypoxemia on cardiovascular responses. Administration of 12 mg of DM i.m. to ewes at 127–133 dGA is followed by fetal hypertension with fetal BP returning to normal within 12 h (19). In this study, we found that maternal DM treatment resulted in fetal hypertension that was short-lived and diminished with subsequent injections. We have investigated the peripheral mechanisms by which glucocorticoids increase BP and have demonstrated an increase in vasoconstriction of small resistance arteries in the fetal sheep in response to endothelin as the fetus matures during the final third of gestation (50), which is mimicked by administration of DM directly to the fetus (51). However, in the adult rat, the pressor effects of ACTH are not ameliorated by endothelin-1 antagonism with bosetan (52). Unlike the actions of mineralocorticoids, glucocorticoid-induced hypertension is not mediated by increased sympathetic tone (53) and in humans is associated with either normal or decreased sympathetic activity (54). In keeping with evidence in humans that suppression of the nitric oxide system may play a role in cortisol-induced hypertension (55–58), we have demonstrated impairment of fetal femoral artery nitric oxide production after three courses of DM administration to the ewe (59).

Fetal hypoxemia has been demonstrated to produce hypertension in fetal sheep >120 dGA (35, 60, 61). Severe maternal hypoxemia induced by apnea has been demonstrated to produce hypertension in nonpregnant ewes (62). In the current study, neither the saline-treated fetuses nor mothers became hypertensive. Akagi *et al.* (30) also demonstrated that maternal and fetal hypoxemia could be induced in sheep at 125 dGA by reducing maternal inspired O_2 content without inducing hypertension. Several studies have shown that late in gestation, fetal hypoxemia does elevate fetal blood pressure (23, 24, 26, 27, 36). In our study, hypertension supervened after hypoxemia in the DM-treated but not control fetuses at 105 dGA, producing the response characteristic of a more mature fetus. This altered response indicates a premature expression of vascular changes that do not normally occur until a later stage of development.

Effects of DM treatment and hypoxemia on organ blood flow. Fetal adrenal blood flow has been shown to be very sensitive to circulating ACTH, and it therefore is not surprising

that fetal adrenal flow fell and vascular resistance increased after DM (63). In contrast, maternal adrenal flow does not seem to be dependent on ACTH concentrations because it was not altered when maternal ACTH fell. DM increased the vascular resistance in the femoral bed in both mother and fetus, again demonstrating the importance of the carcass as a reservoir of peripheral resistance. The major effect of hypoxemia was to further increase vascular resistance in the maternal and fetal femoral vascular beds and decrease fetal cardiac vascular resistance in both groups. DM enhanced the hypoxemia-induced peripheral vasoconstriction, increasing the fetal femoral vascular resistance by 72% as compared with the saline-treated group, in which it increased by 32%. We previously demonstrated that betamethasone given directly to the fetus at 125 dGA decreases fetal cerebral blood flow and blunts hypercapnia-induced vasodilation (15). In contrast, maternal administration at this earlier gestational age seems to provide a slight increase in cortical flow.

In summary, we have reported on the maternal and fetal adrenal responses to hypoxemia after maternally administered DM at 0.7 of gestation. Similar to later in gestation, maternal glucocorticoid administration results in fetal and maternal hyperglycemia as well as cortisol and ACTH suppression. Ewes remained normotensive, whereas fetuses became hypertensive. DM alters fetal responses to hypoxemia in a manner that resembles the changes that occur later in gestation.

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