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Effect of Prostaglandin I_2 on Ovine Maternal and Fetal Adrenal Blood Flows (40674)[1]

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The fetal adrenal has been shown to be instrumental in the initiation of labor in several species (1). The maternal and fetal adrenals have also been shown to be sensitive to vasoactive agents (2–4). Tripp *et al.* (3) reported an increase in fetal adrenal blood flow with prostaglandin E_1 infusion and Flack *et al.* (5) reported an increase in corticosteroidogenesis after prostaglandin stimulation. There are no studies of the response of maternal and fetal adrenals to the same agent. Prostaglandin I_2 is a powerful vasodilator and does not appear to be destroyed by the pulmonary vasculature (6). Prostaglandin I_2 may act as a circulating hormone. For these reasons a series of experiments were performed to compare the maternal and fetal adrenal responses to prostaglandin I_2.

Materials and methods. Surgery was performed on 13 pregnant ewes from 126–129 days of gestation. The sheep were anesthetized with 10 mg/kg Nembutal (Abbott Laboratories) via a jugular catheter and given a spinal anesthetic of 100 mg Xylocaine in 7.5% glucose (Astra). Polyvinyl catheters (1.2 mm o.d., 0.7 mm i.d.) were placed into branches of both maternal femoral arteries and advanced 20 cm. A polyethylene catheter (PE 205), with a polyvinyl catheter inside, was inserted into the common carotid artery and advanced into the left ventricle. The catheter position was confirmed by the characteristic pressure pattern. The abdomen was then opened through a midline incision and the uterus exposed. A fetal hindlimb was brought through an incision in the uterine wall and the ventral surface was anesthetized with subcutaneous Xylocaine. Catheters were placed in the fetal hindlimb artery and vein using polyvinyl catheters similar to those used in the mother. These were advanced approximately 20 cm. The fetal leg incision was closed and another polyvinyl catheter was attached to the surface for measuring intrauterine pressure. The uterus was then closed. All catheters were filled with heparin (100 units/ml) and secured in a pouch on the maternal flank. The maternal jugular and carotid catheters were secured to the neck with an elastic bandage.

Two days after surgery the animal was returned to the laboratory and allowed to stabilize for at least 2 hr before the experiments began. At this point maternal and fetal blood pressures were stable. Maternal and fetal arterial blood samples were taken for blood gas analysis to describe the physiological state of the preparation.

Experimental protocol. Regional maternal and fetal blood flow measurements were made using the microsphere technique as previously described (7, 8). A control injection of radioactive microspheres was given either in the maternal left ventricle or fetal hindlimb vein while withdrawing an integrated arterial blood sample from either the maternal femoral or the fetal hindlimb artery. A bolus injection of prostaglandin I_2 was then given into the maternal left ventricle (1.0 mg) or into the fetal hindlimb vein (0.5 mg). The second microsphere injection was then given 90 sec later at the time of maximum response as indicated by the drop in blood pressure.

The radioactive microspheres were 25 μm in diameter and were labeled with ^{125}I, ^{85}Sr, ^{46}Sc (3M Company), ^{57}Co, or ^{113}Sn (New England Nuclear). The injectate contained approximately 1,000,000 (maternal) or 500,000 (fetal) microspheres labeled with a randomly selected isotope.

The prostaglandin I_2 (Upjohn Company) was stored in a freezer at −20° in vials each containing 5 mg. On the day of the experiment a vial was diluted with 1 ml of ethanol and 4 ml of saline to a concentration of 1 mg/ml, held on ice, and used within 2 hr.

At the completion of the experiment the

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ewe was sacrificed with an overdose of Nembutal (50 mg/ml) followed by an intracardiac injection of saturated KCl. The appropriate tissues were removed, weighed, and placed in vials and counted in a Nuclear Chicago 3 channel gamma counter (Model 1185) with the appropriate integrated blood samples. Blood flows were calculated from the gamma counter output on an interactive computer connection with a Univac 1110 computer on campus. Maternal arterial blood pressure was monitored throughout the experiment. Maternal vascular resistance was defined as the mean arterial blood pressure divided by the blood flow to the organ in question. Fetal blood pressures were taken before and after injections and the average used to calculate resistance. Fetal vascular resistance was defined as the mean arterial minus venous pressure divided by the blood flow to the organ in question. Comparisons were made using the Student's paired or unpaired t test as appropriate and the results were expressed as mean ± SE of the mean.

Results. The maternal adrenal responses are shown in Table I. Blood flow to the maternal adrenal did not change significantly after prostaglandin I_2. However, there was a decrease in the blood pressure from 103.0 ± 5.4 to 64.0 ± 5.7 mm Hg ($P < 0.001$) with an accompanying decrease in adrenal vascular resistance from 72.00 ± 6.65 to 52.60 ± 6.62 mm Hg/(ml/min)/g ($P < 0.001$).

The fetal adrenal responses are shown in Table II. There was a significant increase in blood flow per gram of tissue from 3.36 ± 0.22 to 6.64 ± 0.88 ml/min ($P < 0.01$). The fetal blood pressure decreased from 38.5 ± 1.2 to 28.3 ± 1.8 mm Hg ($P < 0.001$) and the adrenal vascular resistance decreased from 11.76 ± 0.98 to 6.13 ± 1.6 mm Hg/(ml/min)/g ($P < 0.01$). The fetal adrenals had a significantly higher flow per gram of tissue than the maternal adrenals in both the control and test conditions ($P < 0.001$).

The average number of spheres in the fetal adrenals was 887 ± 172 and 1435 ± 197 for the control and test injection, respectively. The fetal integrated blood samples contained 1632 ± 406 spheres and 1273 ± 256 spheres for the control and test conditions, respectively. The number of spheres in the maternal adrenals was 721 ± 105 in the control condition and 533 ± 142 in the test condition. The intergrated control blood samples had 625 ± 209 spheres and 464 ± 131 spheres in the test condition. The maternal arterial blood had a mean pH of 7.56 ± 0.01, pO_2 of 68.8 ± 3.2, and pCO_2 of 22.8 ± 1.0. Blood drawn from the catheter in the fetal hindlimb vein had a pH of 7.39 ± 0.01, pO_2 of 18.5 ± 1.1, and pCO_2 of 35.5 ± 3.9. Average fetal weight was 2.93 ± 0.29 kg.

Discussion. The use of radioactive micro-

TABLE I. MATERNAL ADRENAL CARDIOVASCULAR RESPONSES TO 1.0 MG PROSTAGLANDIN I_2

Sheep No.	Adrenal weight (g)	Blood flow (ml/min × g)		Resistance mm Hg/(ml/min)/g		Blood pressure (mm Hg)	
		Control	Test	Control	Test	Control	Test
1	3.227[a]	1.71	1.63	73.10	49.08	125	80
	4.291	2.05	2.28	60.98	35.09		
2	1.890[a]	2.02	1.49	46.54	29.53	94	44
	2.178	2.11	2.05	44.51	21.46		
3	5.052[a]	1.23	0.96	67.48	87.50	83	84
	4.610	1.31	1.33	63.36	63.16		
4	4.536[a]	0.92	0.51	100.00	94.12	92	48
	4.030	1.05	0.51	87.62	94.14		
5	2.442[a]	2.00	2.00	55.00	30.50	110	61
	1.930	1.72	1.45	63.95	42.07		
6	3.174[a]	0.86	0.90	122.09	66.67	105	60
	2.004	0.91	1.16	115.39	51.72		
7	3.597[a]	2.07	2.14	54.11	32.71	112	70
	3.839	2.08	1.81	53.85	38.67		
Mean	3.343	1.57	1.44	72.00	52.60	103	64
SEM	± 0.294	± 0.13	± 0.16	± 6.65	± 6.62	± 5.4	± 5.7
		$P < .295$		$P < 0.001$		$P < 0.001$	

[a] Indicates left adrenal.

TABLE II. FETAL ADRENAL CARIOVASCULAR RESPONSES TO 0.5 MG PROSTAGLANDIN I_2

Sheep No.	Adrenal weight (g)	Blood flow (ml/min × g)		Resistance mm Hg/(ml/min)/g		Blood pressure (mm Hg)	
		Control	Test	Control	Test	Control	Test
8	0.438	3.998	7.717	8.75	2.85	35	22
9	0.315	3.965	2.790	10.34	11.83	41	33
10	0.367	2.651	9.074	15.09	3.42	40	31
11	0.191	3.351	6.675	10.74	4.35	36	29
12	0.286	2.986	7.531	14.07	10.38	42	31
13	0.246	3.201	6.075	11.56	3.95	37	24
Mean	0.307	3.359	6.644	11.76	6.13	39	28
SEM	± 0.036	± 0.219	± 0.876	± 0.98	± 1.60	± 1.2	± 1.8
		$P < 0.01$		$P < 0.01$		$P < 0.001$	

spheres to measure regional blood flow is a well-established technique. Buckberg *et al.* (9) have stated that a minimum of 400 spheres should be contained in each sample and this criterion has been met in our study. Subdiaphragmatic blood flows in the fetus can be measured with microspheres using the fetal hindlimb artery for the integrated blood sample and the hindlimb vein for the microsphere injections.

Due to our inability to determine fetal weight prior to the experiment and the need to elicit a sizable pressure response, a higher dose of prostaglandin I_2 was given to the fetus. A dose of prostaglandin I_2 was selected which produced approximately the same proportional blood pressure change in the mother and fetus. These values were −37.8 ± 5.1% and −26.5 ± 3.2%, respectively. The higher dosages also ensured the active prostaglandin I_2 was indeed getting to the organ in question, as prostaglandin I_2 is known to have a short half-life. Therefore the magnitude of the responses of the maternal and fetal adrenals to prostaglandin I_2 in these experiments cannot be compared.

The maternal adrenal control blood flow per gram of tissue seen in our study, 1.57 ± 0.13 ml/min×g, is similar to the value of 1.36 ± 0.20 ml/min×g reported by Rosenfeld *et al.* (10).

Tripp *et al.* (3) have reported a twofold increase in fetal adrenal blood flow with prostaglandin E_1 infusion (0.5–5.0 μg/min) in sheep. We observed a similar response to a bolus injection of prostaglandin I_2 in our experiments at a much higher dose (0.5 mg). They reported control flows of 0.8 ± 0.2 mg/min×kg fetus which are higher than ours, 0.40 ± 0.06 ml/min×kg fetus. It would appear that both prostaglandin E_1 and I_2 cause vasodilatation in the vasculature of the fetal adrenal gland.

Prostaglandins may be important in steroidogenesis. Dazord *et al.* (11) have shown that prostaglandin receptors exist in the ovine adrenal glands. An increase in corticosteroidogenesis after prostaglandin administration has been reported in the rat (5, 12), beef adrenal slices (13), and in the sheep fetal adrenals (14). In a study with chronically prepared dogs it was shown that increases in adrenal blood flow elicit increased cortisol secretion (15). Our results suggest that these responses may be associated with prostaglandin-induced hyperemia.

Summary. Fetal (n = 6) and maternal (n = 7) adrenal blood flows were measured with radioactive microspheres in chronically catheterized sheep, before and 90 sec after the injection of prostaglandin I_2. Adrenal vascular resistance is defined as the mean arterial pressure (maternal) or arteriovenous pressure difference (fetal) divided by the adrenal blood flow. Both the mother and the fetus responded with a decrease in blood pressure from 103 ± 5.4 to 64 ± 5.7 mm Hg and 39.0 ± 1.2 to 28.0 ± 1.8 mm Hg, respectively. Adrenal vascular resistance per gram also decreased in the mother from 72.00 ± 6.65 to 52.60 ± 6.62 mm Hg/(ml/min)/g and in the fetus from 11.8 ± 1.0 to 6.1 ± 1.6 mm Hg/(ml/min)/g. Prostaglandin I_2 did not significantly change the flow per gram to the maternal adrenals. The fetal adrenal flow per gram doubled in response to prostaglandin I_2. As the doses of prostaglandin I_2 are dissimilar the magnitude of the changes cannot be

compared. However, prostaglandin I_2 caused vasodilatation in both the maternal and fetal adrenals. Fetal adrenal control blood flows were significantly ($P < 0.001$) greater than the maternal control adrenal blood flows.

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