Insensitivity of the Sheep to Prostaglandins[1] (36986)

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The effects of prostaglandins on the circulation and on uterine activities have been investigated in a variety of animal species, including humans, monkey, rat, guinea pig, dogs, hamsters and rabbits (1). In all of these species, changes in uterine tonus have been produced by PGE_2 and PGF_{2a}. The cardiovascular effects have varied according to the compound used, the dose and the animal species (1).

The pregnant sheep has been the traditional experimental model for the investigation of many aspects of reproduction, particularly those related to uteroplacental–fetal interrelationships. Yet, to our knowledge, the pharmacological effects of prostaglandins have not been investigated in this animal species.

The present report deals with the effects of PGE_2 and PGF_{2a} on the ewe and her fetus when these substances are administered intravenously to the mother or to the fetus.

Materials and Methods. Studies were performed on a total of five near-term pregnant ewes of mixed breed. Each ewe was fasted for 18–24 hr prior to the experiment. The ewe was placed on her left side on the operating table and, under local anesthesia, the right carotid artery and jugular vein were cannulated. The carotid artery catheter served for recording maternal arterial pressure and for collecting arterial blood samples anaerobically. Anesthesia was induced with an initial dose of 6–10 μg/kg of pentobarbital administered through the jugular vein catheter; additional doses were given as needed to maintain an adequate anesthesia. An endotracheal tube was inserted through a tracheostomy and the maternal respiration was supported with compressed air using a positive–negative pressure Bird respirator. In some animals, only the uterine artery supplying the pregnant uterine horn was fitted with an electromagnetic flow transducer, while in others, flow transducers were placed around both arteries. A catheter was placed into a uterine vein branch and was advanced into the main uterine vein; it served for collections of uterine venous blood. A segment of the pregnant uterine horn was exteriorized by laparotomy and was marsupialized to the abdominal walls to prevent evisceration. A catheter was inserted into the amniotic cavity and was held *in situ* by a purse-string suture; it served for monitoring intra-amniotic pressure. In one animal, the fetus was exteriorized and was marsupialized to the uterine incision to protect the umbilical circulation. The fetal head was covered with a saline-filled glove to prevent breathing. A polyethylene catheter was inserted into the fetal femoral artery and was advanced into the descending aorta; it served for arterial pressure recording and for anaerobic collections of blood samples. Another catheter was inserted into the femoral vein and served for drug injections. Electromagnetic flow transducers were placed around the ascending aorta and ductus arteriosus to measure the blood flow in these vessels. Technical details of all these procedures have been published elsewhere (2–4).

All blood flows were measured using cuff-type, balanced field electromagnetic flow transducers and amplifiers previously described (5). Each transducer was selected to fit each vessel snugly but without undue constriction. The transducers were calibrated *in vitro,* and a calibration factor was obtained for each as described in detail elsewhere (6). Blood flow rate in each vessel was calculated from the product of the calibration factor of that particular transducer and the integrated flow

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TABLE I. Effects of Intravenous Injections of Prostaglandins in Pregnant Ewes.[a]

Dose	Art. press. (mm Hg)			Uterine flow (ml/min)		Intra-amniot. press. (mm Hg)		Heart rate (beats/min)		Uter. O_2 Transf. (ml/min)	
μg/Kg.	N[b]	C	A	C	A	C	A	C	A	C	A
Prostg. E_2											
0.4	8	93	96	1514	1470	17	17	144	138	28	29
0.8	10	96	90	1510	1496	16	17	138	133	—	—
1.0	10	86	84	1120	1241	—	—	124	130	32	37
2.0	5	95	100	1241	1300	19	20	130	128	33	38
3.0	7	96	90	1200	1170	—	—	122	116	28	25
5.0	8	90	90	1401	1350	—	—	125	89	—	—
10.0	5	82	65	1250	990	20	24	125	80	24	15
$F_{2\alpha}$											
0.4	10	86	84	685	710	2.5	2.0	160	160	—	—
0.8	7	84	84	730	687	3.0	2.5	170	150	—	—
1.0	9	84	81	710	714	2.5	2.5	158	158	—	—
4.0	6	81	90	660	674	4.0	2.0	142	140	—	—
10.0	6	82	93	630	660	6.0	8.0	—	—	—	—

[a] Values represent average values for each dose administered. C = average control values; A = average readings during 10 min after injection.

[b] N = Number of tests.

deflection (electronic integrator) elicited on the dynograph. The error in this method for any given flow in the great fetal vessels is no more than ±5%. Vascular and intra-amniotic pressures were measured with matched Statham DB-23 strain gauges calibrated to a common zero base line. Phasic and integrated pressure and flow signals were recorded on an Offner dynograph. Fetal effective cardiac output, systemic and uterine vascular resistances were computed by formulas previously described (7). Heart rate was obtained from the phasic pressure or flow records. Maternal and fetal blood pH, pO_2 and pCO_2, percentage saturation, hemoglobin, arteriovenous O_2 content differences were analyzed by techniques previously described (2–4). Uterine oxygen transfer was estimated from the product of flow and A-V O_2.

The experimental protocol comprised the following: A control period of 30 min was observed during which flows and pressures were allowed to stabilize and were recorded continuously: blood respiratory gases and pH were analyzed at 10-min intervals.

A drug-testing period then followed during which doses of prostaglandins[2] E_2 or $F_{2\alpha}$ were administered intravenously to the ewe or to the fetus in single-bolus injections in progressively increasing amounts. The dosage used in the ewe ranged from 0.4 to 10 μg/kg. In the fetus, at the conclusion of the experiment, the fetal weight was obtained and the amounts of the drugs used were converted on the basis of body weight; a dosage range of 0.5 to 100 μg/kg of body weight was obtained. The effects of each injection on flows and pressures were monitored continuously. Adequate time was allowed between subsequent injections for the pressures and flows to return to control values. Blood respiratory gases and pH were analyzed at frequent intervals.

In addition to single intravenous doses, the effects of continuous infusion of prostaglandin E_2 were tested. In this case, the drug was administered via the femoral vein at rates of 10 μg/min for 20 min. Flows and pressures were monitored continuously before, during and after interruption of the infusion.

Results. I. Effects of Prostaglandins E_2 and $F_{2\alpha}$ When Injected into the Mother. Table I presents the data on the effects of intermittent bolus injections of PGE_2 and $F_{2\alpha}$ on maternal arterial pressure, heart rate, utero-

[2] Courtesy of Upjohn Laboratories.

TABLE II. Effects of Intravenous Infusion of Prostaglandin E_2 on the Pregnant Ewe.[a]

Time (min)	Art. press. (mm Hg)	Heart rate (beats/min)	Intra-amniot. press. (mm Hg)	Total uterine flow (ml/min)
Control	93	145	18	1285
	Infusion of prostgl. 10 μg/min			
2	96	154	17	1403
4	96	152	17	1450
6	96	152	17	1472
8	99	144	17	1472
10	99	144	17	1446
14	102	144	17	1397
18	102	148	17	1446
25	96	148	17	1493
30	96	148	16	1514

[a] Ewe's wt: 55 kg.

placental blood flow, uteroplacental oxygen transfer and intra-amniotic pressure.

Acute injections of PGE_2 and $F_{2\alpha}$ into the mother in doses varying between 0.4 and 10.0 μg/kg of the ewe's body weight produced no significant change in maternal cardiovascular functions; arterial pressure, heart rate, uterine blood flow, intra-amniotic pressure and uteroplacental oxygen consumption showed negligible changes (Table I). Blood pO_2, pCO_2 and pH remained within control ranges. Likewise, continuous infusion of PGE_2, in doses of 10 μg/min produced no significant change in maternal arterial pressure, heart rate, intra-amniotic pressure and total uterine blood flow (Table II).

II. Effects of Prostaglandin $F_{2\alpha}$ When Injected into the Fetus. Intravenous administration of $PGF_{2\alpha}$ into the near-term fetal lamb in dosages varying from 0.5 to 100 μg/kg had no significant effects on fetal cardiovascular functions. Arterial pressure, heart rate, ductus arteriosus and ascending aortic flows, and the effective cardiac output remained essentially unchanged (Table III). Blood pO_2, pCO_2 and pH remained within control ranges.

Discussion. Numerous reports have shown that prostaglandins elicit myometrial contractions *in vivo* as well as *in vitro*. In human subjects, as well as in rats, mice and monkeys, these substances produce abortion or induce parturition (1).

In sheep, Liggins and Grieves (8) observed a rise in prostaglandin concentration in uterine venous blood as well as in myometrial and maternal placental tissues following administration of dexamethasone to the fetus. On the basis of these findings, these authors postu-

TABLE III. Effects of Prostaglandin $F_{2\alpha}$ when Administered to the Fetus on the Fetal Circulation.[a]

Dose (μg/kg)	Heart rate (beats/min)		Arterial press. (mm Hg)		Duct. art. flow (ml/min)		Ascend. aort. flow (ml/min)		Eff. card. outp (ml/min)	
	C	A	C	A	C	A	C	A	C	A
0.5	234	237	57	57	270	294	525	491	795	785
1.0	240	238	57	57	294	307	490	491	784	798
2.0	228	234	54	58	358	370	446	424	804	798
4.0	234	240	58	54	218	243	535	535	753	778
8.0	244	240	59	58	414	395	379	357	793	752
16.0	240	238	59	58	395	395	357	335	752	730
100.0	232	236	58	57	395	376	335	312	730	688

[a] C = average control readings; A = average readings for 10 min after injection.

lated that prostaglandins may play an important role in initiating labor in this species. This hypothesis is based on the assumption that high levels of glucocorticoids in the fetal blood stimulate prostaglandin production in the mother which, in turn, triggers labor.

Our data do not provide support for this hypothesis. Our failure to elicit any change in uterine tone in the intact pregnant sheep at term with exogenous administration of large doses of PGE_2 and PGF_{2a}, casts doubts about the sensitivity of the pregnant uterus to these substances in this animal species.

The insensitivity of the sheep to prostaglandins is further supported by the lack of any cardiovascular response, either in the ewe or in the lamb, to large doses of these compounds. The absence of any change in the arterial pressure and uteroplacental blood flow, as well as in the fetal vascular pressures, ductus and ascending aortic flows, is in striking contrast to the cardiovascular effects produced by these substances in other animal species (1, 9–13).

The apparent insensitivity of the sheep to prostaglandins could have been related to a possible loss of pharmacological activities of the particular batch used in these experiments. This possibility, however, was ruled out as the unused portion of the preparations were tested by standard techniques in the Upjohn Laboratories. These analyses showed normal pharmacological activities.

Summary. Administration of prostaglandins E_2 and F_{2a} to near-term pregnant sheep failed to produce any effects on uterine tone and on maternal cardiovascular functions. Likewise, the administration of these substances to the fetal lamb failed to alter the fetal vascular pressures and cardiac output. It is concluded that the sheep are insensitive to prostaglandins.

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