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THE EFFECT OF PROSTAGLANDIN INHIBITION

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ABSTRACT The effect of 8 mg/kg of indomethacin on uterine blood flow, prostaglandin production, and intraamniotic fluid pressure was examined in late pregnant dogs. Uterine blood flow was measured with 15 μm radiolabeled microspheres. Because we found that a significant percentage of the microspheres shunted through the placental circulation into the lungs, we calculated placental blood flow by adding the shunted microspheres through the placenta to the nonshunted microspheres in the placenta. Total uterine blood flow significantly increased from 271±69 ml/min during control period to 371±72 ml/min ($P < 0.01$) 30 min after indomethacin. This increase was attributable to the change in blood flow to the placental circulation (222 ±58 to 325±63 ml/min; $P < 0.01$). Associated with these hemodynamic changes we found an almost complete suppression of uterine prostaglandin E_2 production (1,654±305 to 51±25 pg/ml; $P < 0.01$) as measured by gas chromatography-mass spectrometry. In addition, we found that indomethacin treatment resulted in uterine relaxation as measured by intraamniotic fluid pressure changes (11.2±1.3 mm Hg to 8.5 ±1.2 mm Hg; $P < 0.001$).

We conclude that indomethacin causes an increase in placental blood flow without any change in flow to the rest of the uterus, and that this dose of the drug inhibits greater than 95% of uterine prostaglandin production. In addition, indomethacin is responsible for uterine relaxation. The increase in placental blood flow after indomethacin is probably a result of uterine relaxation, which is secondary to prostaglandin synthesis inhibition.

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INTRODUCTION

During pregnancy and parturition there are changes in the prostaglandin system that have suggested a potential physiological role for these fatty acids; however, their exact role is undefined. With rhesus monkeys, Novy et al. showed that indomethacin, an inhibitor of prostaglandin synthesis, blocked the normal onset of parturition (1). Zuckerman et al. later reported that indomethacin was successful in arresting premature labor in women whose cervix was less than 3 cm dilated and produced minimal side effects to the mother and fetus (2). Wiqvist et al. confirmed Zuckerman's findings, again showing indomethacin to be reasonably safe in the third trimester of pregnancy (3). With the proposed clinical use of the nonsteroidal anti-inflammatory drugs in premature labor, it became important to determine whether uterine blood flow was altered because placental vascular insufficiency is a well known cause of fetal distress. Terragno et al. (4) and Venuto et al. (5) have claimed that indomethacin is a potent vasoconstrictor of uterine blood flow in dogs and rabbits, respectively, and for this reason might be contraindicated in pregnancy. Although there is some interspecies variation in placental blood flow, it is surprising that the clinical findings have not suggested placental vascular insufficiency as a side effect of indomethacin.

Certain anatomic and physiologic observations indicate that indomethacin may not, in fact, constrict the uteroplacental circulation. The placenta, unlike most other circulatory beds, does not have capillaries, but is fed by the spiral arteries arising from the distal myometrium (6, 7). The spiral arteries feed directly into the intervillous spaces where maternal and fetal exchange of nutrients occurs. Spiral arteries histologically show musculoelastic degeneration most pronounced in the endometrium but also present in the myometrium (8). Because the spiral arteries have very little smooth muscle, thus poor intrinsic tone, placental circulation must be at least partially dependent upon myometrial tone. This supposition is supported by Novy et al. who demonstrated an inverse relationship between placental blood flow and intraamniotic fluid pressure in rhesus monkeys (9). If nonsteroidal anti-inflammatory drugs relax the uterine myometrium by reducing local production of prostaglandins, as has been suggested by others (10–15), it would follow that placental blood flow should be increased when prostaglandin synthesis is inhibited. We tested this hypothesis with late pregnant dogs.

METHODS

A total of 10 late pregnant mongrel dogs was used for two sets of experiments.

Hemodynamic methods. Six late pregnant dogs weighing between 14 and 28 kg were used to measure hemodynamic parameters and prostaglandin levels. The dogs were anesthetized with 30 mg/kg pentobarbital, intubated, and ventilated with a positive pressure respirator. One femoral vein was cannulated for drug administration, and both femoral arteries were cannulated, one for continuous blood pressure monitoring, and the other for reference blood sample withdrawal at the time of microsphere injection. The left carotid artery was exposed and a catheter was passed retrograde into the left ventricle for administration of radioactive microspheres. Through a midabdominal incision the uterus was exposed, and one of the major uterine veins was cannulated from a smaller venous branch to sample venous blood for prostaglandin measurement as described below.

After the surgery, we allowed ~1 h for stabilization. The experiment was divided into three periods. The first period was a control; the second was 30 min after 8 mg/kg of intravenous indomethacin (dissolved in sodium carbonate buffer); and the third period followed ligation of the uterine circulation and removal of the pregnant uterus.

The pregnant uteri were removed by carefully dissecting and doubly ligating the vasculature closely along the uterine walls. Only the vasculature going to or coming from the uterus per se was obstructed. The other pelvic vasculature was left intact during the entire dissection. The total amount of blood lost, excluding what was trapped in the uterus, was minimal. The entire excision of the uterus took ~ 30 min.

During each period 200,000–1,000,000 microspheres (15 ±3 μm, 3M Co., St. Paul, Minn.), labeled with one of three nuclides (^{95}Nb, ^{85}Sr, ^{51}Cr), were suspended in saline in an injection chamber, sonicated to disperse the beads, and injected over 10 s into the left ventricle. A reference arterial sample was withdrawn by a constant withdrawal pump at a rate of 10–20 ml/min for 60 s beginning at the start of the microsphere injection. Cardiac output was calculated by multiplying total radioactivity injected by reference sample withdrawal rate divided by the radioactivity of the reference blood sample. 15–20 min after the last microsphere injection the animal was sacrificed and the lungs, placenta, and the rest of the uterus was dissected, weighed, and counted in a gamma scintillation counter equipped with multichannel analyzer (Packard Instrument Co., Inc., Downers Grove, Ill.). The method of calculating the radioactivity for a given nuclide in the presence of other nuclides has been published (16). The intervillous space of the placenta offers very little resistance to the 15-μm microspheres; thus, we found that most of the spheres pass through the placental circulation and lodge in the lungs. We devised a method to measure placental blood flow taking advantage of the shunt. Assuming the shunt is entirely through the placenta, the placental blood flow can be calculated by determining the extrauterine, arterial-venous shunt in each dog after complete interruption of the uteroplacental circulation (period 3) and by the following formula: placental blood flow = PR + (TLR − ELR) × cardiac output. PR = placental radioactivity; TLR = total lung radioactivity with uteroplacental circulation intact; ELR = fraction of radioactivity in the lungs that is extrauterine. The extraplacental uterine blood flows was calculated from the fraction of radioactivity in the rest of the uterus multiplied by the cardiac output.

Intraamniotic fluid pressure measurements. Four late pregnant dogs were anesthetized with pentobarbital 30 mg/kg, intubated, and ventilated with a positive pressure respirator. The femoral artery and vein were cannulated for continuous blood pressure monitoring and drug administration. Through a midline low-abdominal incision the pregnant uterus was exposed and one fetus identified. A catheter was passed into the amniotic sac until there was free flow of amniotic fluid; catheter was then attached to a pressure transducer to monitor amniotic fluid pressure. The abdomen was closed, and the animal was allowed to stabilize. The experiment consisted of an initial control period of 2 h followed by the administration of 8 mg/kg of indomethacin intravenously with continuous recording of the intraamniotic fluid pressures.

Prostaglandin analysis. In the six pregnant dogs from the hemodynamic studies, 12–15 ml of blood was drawn from the aorta and uterine vein into plastic syringes containing 0.1 vol of 3.8% sodium citrate and 1% indomethacin during the control period, and 30 min after 8 mg/kg of indomethacin. The blood was immediately transferred to a glass centrifuge tube, cooled to 0–5°C, and the plasma isolated by centrifugation at 8,000 *g* for 15–20 min. The plasma volume and hematocrit were recorded and the plasma transferred to a 100-ml centrifuge tube. Internal standards and radioactive tracers were added to the plasma before freezing at −20°C. The internal standards employed were 3,3,4,4-tetradeutero-analogues of PGE_2[1] (prostaglandin E2, 1,500 ng) and 15 keto-13,14-dihydro (15 KH_2) PGE_2 (1,200 ng) (generous gifts of the Upjohn Co., Kalamazoo, Mich. Dr. U. Axen). Approximately 150,000 dpm of each of the tritiated analogues (120,000–170,000 mCi/mmol, Amersham Corps., Arlington Heights, Ill.) were added as tracers to facilitate isolation and purification of the prostaglandins.

The prostaglandins were extracted into chloroform in acid pH (pH 3.0) and the methyl esters formed with diazomethane. Initial purification and chromatographic separation of PGE_2-methyl ester and 15-keto-13,14-dihydro PGE_2-methyl ester were achieved via high performance liquid chromatography as described by Hubbard and Watson (17). Final purification and quantification of PGE_2 and 15 KH_2E_2 was achieved via combined gas chromatography-mass spectrometry with selected ion monitoring. Before gas chromatography-mass spectrometry analysis, PGE_2-methyl ester was converted to the O-methoxime-bis-acetate derivative. 15 KH_2E_2-methyl ester was converted to the bis-0-methoxime-trimethylsilyl ether derivative. Gas chromatography-mass spectrometry analysis of the derivatized PGE_2 and 15 KH_2E_2 was accomplished on a Hewlett-Packard model 5982A gas chromatograph-mass spectrometer (Hewlett-Packard Co., Palo Alto, Calif.) equipped with a dual electron ionization-chemical ionization source and a membrane separator. The mass spectrometer was equipped with an ion selector device (Hewlett-Packard Co.) for manual operation of selected ion monitoring with a conventional strip chart recorder. The electron energy was 70 eV and the emis-

[1] *Abbreviations used in this paper:* PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$.

TABLE I
Blood Flow and Hemodynamic Parameters before and after Intravenous Indomethacin (I)

	Total uterine				Placental				Rest of uterine							
	Flow		Resistance		Flow		Resistance		Flow		Resistance		Mean arterial		Cardiac output	
Dog	Control	After I	Control	After I	Control	After I	Control	After I	Control	After I	Control	After I	Control	After I	Control	After I
	ml/min		*mm Hg/ml/min*		*ml/min*		*mm Hg/ml/min*		*ml/min*		*mm Hg/ml/min*		*mm Hg*		*ml/min*	
1	224	405	0.513	0.304	190	361	0.605	0.341	34	44	3.38	2.79	115	123	2,230	1,770
2	159	210	0.622	0.586	103	186	0.961	0.661	56	24	1.77	5.12	99	123	1,370	972
3	376	521	0.335	0.249	313	482	0.402	0.270	63	39	2.00	3.33	126	130	2,680	2,375
4	131	171	0.786	0.604	110	146	0.936	0.733	21	31	4.90	3.45	103	107	1,200	841
5	567	619	0.238	0.231	466	518	0.290	0.276	101	101	1.34	1.42	135	143	2,542	2,765
6	171	295	0.830	0.518	148	258	0.959	0.593	23	37	6.17	4.13	142	153	1,033	1,463
Mean	271	371	0.554	0.415	222	325	0.692	0.479	50	46	3.26	3.37	120	130	1,842	1,697
SEM	69	72	0.097	0.075	58	63	0.123	0.085	12	11	0.79	0.51	7	7	296	312
P	<0.01		<0.05		<0.01		<0.01		NS		NS		<0.05		NS	

NS = no significant change.

sion current was 200 μA. The analyzer temperature was 100°C. The interface line between the gas chromatograph and the mass spectrometer was maintained at 300°C. Helium at a flow rate of 20–30 ml/min was used as a carrier gas.

For analysis of the derivatized PGE_2, a silanized glass column (1 M × 3 mm) of 3% OV-1 on Gas Chrom Q 100/120 (Applied Science Laboratories, Inc., State College, Pa.) at an oven temperature of 250°C was employed. For the analysis of the derivatized 15 KH_2E_2, a silanized glass column (1 M × 3 mm) of 1% Dexsil 300 on Chromosorb W 100/120 (Applied Science Laboratories, Inc.) at an oven temperature of 235°C was employed. The ion pair for selective ion monitoring analysis of the derivatized PGE_2 and its internal standard was mass/charge 419 and 423. The ion pair for selective ion monitoring analysis of the derivatized 15 KH_2E_2 and its internal standard was mass/charge 375 and 379. The detection limits of these assays are 100 pg/ml for PGE_2 and 50 pg/ml for 15 KH_2E_2. The net prostaglandin levels were calculated by substracting arterial from venous blood levels.

Statistics. Data were analyzed with Student's *t* test for paired comparisons, comparing control results to the results 30 min after 8 mg/kg of indomethacin.

RESULTS

In the six dogs studied, 30 min after indomethacin the total blood flow to the uterus increased significantly from a mean of 271±69 to a mean of 371±72 ml/min (Table I). Even though the arterial pressure increased after indomethacin, the uteroplacental vascular resistance significantly decreased indicating vasodilation. There was also no significant change in cardiac output to explain changes in flow (Table I). The increase in uteroplacental blood flow was entirely due to the significant increase in placental blood flow, as the flow to the remainder of the uterus showed no consistent change after 8 mg/kg of indomethacin (Fig. 1). Placental blood flow accounted for 81% of the total uterine blood flow which is in agreement with the literature (18). Uterine blood flow represented 14.2% of the total cardiac output which is also in agreement with the literature (19, 20). Because the present methodology for measuring uterine blood flow is novel, we measured the right uterine arterial blood flow electromagnetically (Statham Instruments, Inc., Oxnard, Calif.) in two additional pregnant mongrel dogs. In both dogs indomethacin increased the right uterine arterial blood flow within 30 min (60 ml/min control to 85 ml/min after indomethacin and 90 ml/min control to 110 ml/min after indomethacin).

Associated with the change in blood flow, the PGE_2 concentrations were suppressed by more than 95% 30 min after 8 mg/kg of indomethacin (Table II). The concentration of major metabolite, 15 keto-13,14-dihydro PGE_2, was also depressed in parallel with PGE_2 in-

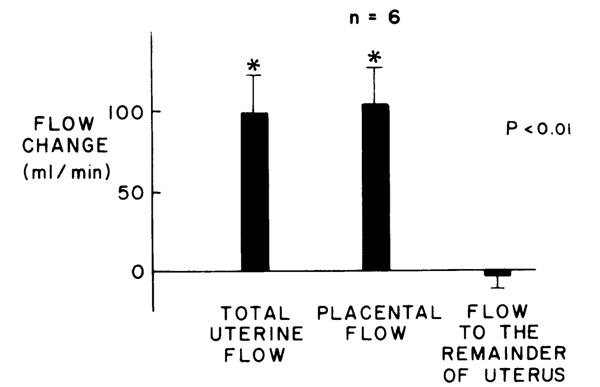

FIGURE 1 Indomethacin's effect on blood flow to the entire uterus, placenta, and the remainder of the uterus. Bar graphs represent mean changes in blood flow in millimeters per minute ±1 SE.

TABLE II
Prostaglandin Measurements

Dog	PGE_2		15 Keto dihydro PGE_2	
	Control	After indomethacin	Control	After indomethacin
		*pg/ml**		
1	578	0	693	0
2	2,156	145	1,011	10
3	1,660	0	1,166	0
4	2,293	74	4,085	779
5	921	85	1,050	110
6	2,317	0	2,130	150
Mean	1,654	51	1,689	175
SEM	305	25	518	123
P	<0.01		<0.02	

* Net concentration (venous − arterial).

dicating that decreased levels of PGE_2 were not because of altered metabolism. In these six dogs, and subsequently in 4 more late pregnant dogs, we also measured uterine venous concentration of $PGF_{2\alpha}$ (prostaglandin $F_{2\alpha}$) and 15 keto dihydro $PGF_{2\alpha}$ by gas chromatography-mass spectrometry. We could not detect any $PGF_{2\alpha}$ or its metabolite, in agreement with Wiqvist et al. (21) that $PGF_{2\alpha}$ production is a labor-related event. The sensitivity of our assay was 50 pg/ml.

Because various nonsteroidal, anti-inflammatory drugs have been reported to be associated with uterine relaxation (10–12, 14, 15), we looked at the effect of indomethacin in this regard. Before indomethacin the amniotic fluid pressure showed small rhythmic variations, but the mean pressure remained constant during the 2-h control period. After indomethacin the amniotic fluid pressure decreased over 30 min and lost its rhythmicity (Table III). At no time after indomethacin was the amniotic fluid pressure higher than the lowest pressure recorded before indomethacin. We chose 30 min because that is the time we measured the effects of indomethacin on uteroplacental hemodynamics and prostaglandin synthesis. It thus appears that indomethacin in late pregnancy decreases uterine tone as measured by intraamniotic fluid pressure.

DISCUSSION

The importance of uteroplacental prostaglandin production during pregnancy is unclear. Initial animal studies and later clinical studies showed that inhibition of prostaglandin synthesis in late pregnancy is not associated with fetal death in utero (2, 3, 11, 22) but may result in premature closure of the ductus arteriosus (23–26). The role of prostaglandins in labor is more clear-cut. Not only do indomethacin and other nonsteroidal anti-inflammatory drugs inhibit the onset of labor (1, 27–29), but large surges of $PGF_{2\alpha}$ and its metabolite have been measured in the blood at the initiation of labor (21). $PGF_{2\alpha}$ levels before labor, even in late pregnancy, are very low, whereas the concentrations of PGE_2 in human amniotic fluid, in rabbit uterine vein, and dog uterine vein have all been reported to be high during the latter stages of pregnancy (30, 31, 4). Therefore, it appears that, of the prostaglandins studied, PGE_2 is being produced by the uteroplacental unit in measurable quantities in late pregnancy, whereas $PGF_{2\alpha}$ production is related to the onset of labor. Our data are in agreement with the literature in this regard.

The exact site of PGE_2 production in the feto-placental unit is not known. PGE_2 is very potent in producing contraction of the pregnant uterus (32). If PGE_2 is either produced in the myometrium or comes in contact with the myometrium, it is quite likely that PGE_2 would contribute to the myometrial tone in late pregnancy. Our intraamniotic fluid pressure data in dogs would support this concept. The fact that myometrial tone is a determinant of placental blood flow has been studied by several investigators. Novy found that myometrial contraction produced by exogenously administered PGE_2 is associated with a large drop in placental blood flow in pregnant monkeys (9). In fact, he was able to establish an inverse linear relationship between uterine blood flow and intraamniotic fluid pressure. Also, angiographic studies in pregnant women and monkeys have shown that blood flow to the placenta is markedly suppressed during uterine contraction (33, 34). Blood flow to the placenta is not constant as in organs with capillary beds but occurs in spurts through the spiral arteries, and these spurts decrease or disappear during contraction of the pregnant uterus. A recent report by Rankin and Phernetton (19) also showed that PGE_2 infused into the ovine maternal arterial system causes myometrial contraction and a decrease in uterine blood flow. However, infusion of PGE_2 into the fetus caused a minimal increase in maternal uterine and renal blood flow. Because the placenta is rich in the degradative enzyme, 15-hydroxy

TABLE III
Mean Intraamniotic Fluid Pressure

Dog	Control	After indomethacin
	mm Hg	
1	15	12
2	9	7
3	11	7.5
4	10	7.5
Mean	11.2	8.5
SEM	1.3	1.2
P	<0.001	

prostaglandin dehydrogenase, PGE_2 may not cross the placenta intact. Also, because the placental exchange sites are not associated with resistance vessels in the uterus, one would have to postulate that a circulating vasoactive substance caused the hemodynamic changes described. Because no measurements of vasoactive substances were made in these sheep, we cannot identify the substance that escaped metabolism by the placenta and maternal lung and recirculated to produce a decrease in renal and uterine vascular resistance. It is unlikely that PGE_2 is the substance because it should have been catabolized by the placenta and lung, and even if it escaped metabolism, PGE_2 in the maternal arterial system would result in a decrease in uterine blood flow as described by Rankin and Phernetton (19).

Our data are consistent with the interpretation that myometrial tone plays a key role in regulation of placental blood flow. With 8 mg/kg of indomethacin intravenously, we were able to observe placental vasodilation at a time that prostaglandin production was almost completely inhibited. Whether the vasodilation and myometrial relaxation was secondary to a decrease in prostaglandin production is only inferential. However, we know that PGE_2 is a potent myometrial stimulant, and associated with its inhibition we observed two physiological events: placental vasodilation and myometrial relaxation.

The 24% decrease in intraamniotic fluid pressure is compatible with a 25% fall in uterine vascular resistance based on the report of Novy et al. who observed a 50% increase in uterine blood flow in the pregnant monkey associated with a 33% decrease in intraamniotic fluid pressure (9). In addition, the decrease in uterine blood flow after myometrial contraction may not occur simply from altered tissue pressure alone, but also from changes in geometric configuration of the pregnant uterus during contraction, resulting in folding parts of the vasculature with a resultant obstruction of blood flow.

Terragno et al. (4) and Venuto et al. (5) have reported a large fall in uterine blood flow after administration of indomethacin to the pregnant dog and pregnant rabbit, respectively. Because their results were diametrically opposed to ours, we examined their reports to determine the reasons for the discrepancy. Terragno et al. administered indomethacin (in 10% alcohol in Kreb's solution) intravenously until they observed a decrease in uterine blood flow by more than 20%. They found that the dose of indomethacin required to produce a reduced uterine blood flow was quite variable, and as high as 120 mg/kg was required. They concluded that the canine pregnant uterus was more resistant to inhibition of prostaglandin synthesis than the canine kidney. Because the end point of their experiment was blood flow reduction and not prostaglandin inhibition, it is difficult to accept their conclusion that the pregnant uterus is resistant to inhibition of prostaglandin synthesis. We found that 8 mg/kg indomethacin was more than adequate to decrease uterine prostaglandin output by greater than 95% in all dogs. We wonder if the very high doses of indomethacin used by Terragno et al. were not systemically toxic to the dogs resulting in large decreases in cardiac output (not measured) and, consequently, a reduced uterine blood flow.

Venuto et al. used 15-μm microspheres to measure blood flow but failed to account for the shunt of microspheres through the placental circulation. Because they did not measure the lung radioactivity, there is no way to determine the actual placental blood flow. Consequently, their uterine blood flow results were very low compared to other studies. They report an average of only 5% of the cardiac output going to the uterus in late pregnancy, whereas studies in sheep, rabbits, and our data in all dogs all show about 15–20% of the cardiac output is delivered to the pregnant uterus late in pregnancy (20, 35). Table IV shows that in our dogs after indomethacin, 16.8% of the microspheres lodge in the lungs, but after uterine blood flow interruption this is reduced to 2.9%. Because the shunt increased with indomethacin treatment it is impossible to interpret the effects of indomethacin reported by Venuto et al.

In accord with our data, a recent report by Speroff et al. disputes the notion that indomethacin causes severe uterine vasoconstriction. In their pregnant monkeys, these investigators found that indomethacin treatment was associated with an increase of uterine blood flow in three of four animals (36).

We conclude from our data that indomethacin is a placental vasodilator probably as a result of uterine relaxation, which is secondary to prostaglandin synthesis inhibition. We believe these data have clinical relevance for the use of nonsteroidal, anti-inflammatory drugs in premature labor. Our data also explain why neither Zuckerman et al. nor Wiqvist et al. found sig-

TABLE IV
Radioactivity in the Lung after Interruption of Uterine Circulation

Dog	Control	After indomethacin	After flow interruption
		%	
1	7.0	15.1	0.0
2	6.0	12.5	1.0
3	12.3	20.9	4.1
4	10.7	15.6	4.1
5	13.8	13.2	1.8
6	20.5	23.2	6.5
Mean	11.7	16.8*	2.9*
SEM	2.1	1.8	1.0
P		<0.05	<0.05

* $P < 0.05$ as compared to control.

nificant fetal distress associated with prostaglandin synthesis inhibition.

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