Uterine Blood Flow, Oxygen and Glucose Uptakes at Mid-Gestation in the Sheep (43158AA)

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Abstract. **In early ovine fetal development, the placenta grows more rapidly than the fetus so that at mid-gestation the aggregate weight of placental cotyledons exceeds fetal weight. The purpose of this study was to compare two separate methods of measuring uterine blood flow and glucose and oxygen uptakes in seven mid-gestation ewes, each carrying a single fetus. Uterine blood flow to both uterine horns was measured by microsphere and by tritiated water steady-state diffusion methodology. Calculations of tritiated water blood flows and oxygen and glucose uptakes were based on measurements of arteriovenous concentration differences across each uterine horn. The distribution of blood flow and oxygen uptake between the two uterine horns was strongly correlated with placental mass distribution. The two methods gave comparable results for uterine blood flow (457 ± 35 vs 476 ± 35 ml/min), oxygen uptake (457 ± 35 vs 476 ± 35 μmol/min), and glucose uptake (63 ± 8 vs 64 ± 6 μmol/min). Uterine blood flow was approximately 38% of the late gestation value and 56.1 ± 1 times higher than umbilical blood flow. Uteroplacental oxygen consumption was about 58% of late gestation measurements and 3.9 ± 0.5 times higher than fetal oxygen uptake. We confirm that the large placental mass of mid-gestation is associated with high levels of maternal placental blood flow and placental oxidative metabolism.** [P.S.E.B.M. 1990, Vol 195]

At mid-gestation the ovine placenta attains its maximum size and weighs more than the fetus. From mid-gestation to term, placental weight declines slightly while fetal weight increases 15- to 20-fold so that near-term placental weight has become one-tenth or less of fetal weight. The metabolic and circulatory implications of these marked differences in placental and fetal growth are not clear because most studies of uteroplacental perfusion and metabolism under normal physiologic conditions have been limited to late gestation.

Studies in late gestation have utilized the steady-state diffusion technique (1) for the purpose of estimating uterine and umbilical blood flows and substrate uptake and transport by the uteroplacenta (2). Recently, it became possible to perform similar studies in the unstressed pregnant ewe at mid-gestation (3). These studies, however, were focused primarily on umbilical blood flow and fetal metabolism (3, 4) and did not attempt to validate the methodology in relation to measurements of uteroplacental blood flow and substrate uptake. In singleton pregnancies there is histologic evidence indicating slower placental development in the uterine horn that does not contain the fetus at less than 70 days of gestation (5). Uneven placental development could create in early gestation large inequalities in the arteriovenous differences of the blood flow indicator and the metabolic substrates across the circulation of the two uterine horns.

The purpose of this study was to compare two separate methods of measuring uterine blood flow and uptake of glucose and oxygen by the pregnant uterus in the mid-gestation ewe carrying a single fetus. We sampled simultaneously the venous drainage of the two uterine horns and measured uterine blood flow by the radioactive microsphere technique and by the steady-state diffusion method using tritiated water as the test molecule.

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Materials and Methods

Surgery and Animal Care. Seven mixed breed (Columbia-Rambouillet) ewes at 69–72 days' gesta-

tional age at surgery and carrying a single fetus were used in this study. These pregnancies were time dated (Nebecker Ranch, Inc., Lancaster, CA). Three ewes were homozygous for hemoglobin B, one was homozygous for hemoglobin A, and three were AB heterozygous. The animals were fasted for 48 hr prior to surgery. Under intravenous pentobarbital sedation and tetracaine hydrochloride (10–12 mg) spinal anesthesia, polyvinyl catheters (0.034-in. i.d.) were placed in the major uterine vein draining the horn containing the singleton fetus (H_f) and in the major uterine vein draining the nonfetal horn (H_{nf}). Catheter tips were located 4–5 cm inferior to the level of the ovaries and distal to any apparent venous tributaries.

A uterine incision was made in the fetal horn and polyvinyl catheters (0.023-in i.d.) were placed for blood sampling in the cotyledonary branches of the umbilical artery and vein with tips positioned in the major umbilical vessels as described previously (3). A catheter was placed into the amniotic cavity of the fetal horn for installation of antibiotic. A second incision was made in the nonfetal uterine horn and a polyvinyl catheter (0.023-in i.d.) for infusion was placed in a cotyledonary branch of the umbilical vein. After closure of the uterine incisions and abdominal cavity, polyvinyl catheters were placed in the left maternal femoral artery (0.045-in i.d.) for sampling and the right maternal carotid artery (0.06-in i.d.) for infusion of microspheres. The tip of the carotid artery catheter was positioned in the left ventricle. The carotid catheter was loosely wrapped around the ewe's neck and secured with tape. All other catheters were tunneled subcutaneously to an external flank pouch.

The animals recovered promptly from surgery and were standing and feeding in individual carts within 6 hr. The catheters were flushed with heparinized saline. Ampicillin (500 mg) was infused via the amniotic catheter on the day of surgery and with each flushing of the catheters postoperatively. The ewes were given water and fed *ad libitum* with dehydrated alfalfa pellets.

Experimental Design. Each study was conducted after a minimum of 5 days of recovery from operative stress between 74 and 79 days of gestation. A solution of ^3H_2O (20 $\mu Ci \cdot ml^{-1}$; Amersham, Arlington Heights, IL) in saline was infused into the fetus via the cotyledonary branch of the umbilical vein in H_{nf} at a rate of 1.6 $\mu Ci \cdot min^{-1}$ (0.08 $ml \cdot min^{-1}$). After at least 60 min of ^3H_2O infusion to reach steady state of ^3H_2O concentrations, blood samples for plasma ^3H_2O concentration and whole blood oxygen capacity, oxyhemoglobin saturation, and glucose concentration were withdrawn simultaneously from the maternal arterial, the two uterine venous, and the umbilical arterial and venous catheters. Six such sets of samples were obtained over 1.5–2 hr, three sets of which were obtained before the microsphere injection and three sets after.

Gadolinium-153-labeled microspheres (Dupont NEN, Boston, MA) with a diameter of 25 μm were injected into the left ventricle of the ewe's heart midway through the study period. The estimated total number of spheres injected was at least $1.6–2.2 \times 10^6$ per animal. Each animal received a single injection over approximately 90 sec. Blood was withdrawn from the maternal femoral artery at a rate of 4 $ml \cdot min^{-1}$ beginning 15–30 sec before microsphere injection and continuing for 60–90 sec after the completion of microsphere injection.

The ewe was sacrificed with an euthanasia solution (T-61; Taylor Pharmaceutical Co., Decatur, IL) on the day of study. The fetus, endomyometrium of each uterine horn, and placental cotyledons within each horn were separately weighed and all catheter locations were confirmed at autopsy.

Analytical Methods. Microsphere radioactivity in tissues and the reference blood sample was determined with a three-channel gamma counter (Nuclear-Chicago Corp., Des Plaines, IL). Radioactivity in the entire cotyledonary mass was counted. The endomyometrium of each uterine horn was homogenized separately and five aliquots of homogenate from each horn were counted. Care was taken to ensure that the tissue height in each counting vial was no greater than 2 cm (6). The coefficient of variation of endomyometrial counts ($cpm \cdot g^{-1}$) was 11%.

Plasma ^3H_2O concentration was measured after incubation in 1.0 ml of Protosol to solubilize the proteins. PCS liquid scintillation fluid (15 ml; Amersham) was added and the radioactivity was counted approximately 24 hr later by means of a Packard Tri-Carb 460 C liquid scintillation counter with internal quench correction. Plasma radioactivity $(^3H_2O)_P$ was converted to whole blood radioactivity $(^3H_2O)_B$ as described elsewhere (3).

Whole blood oxygen content (mM) was calculated as the product of the blood oxygen capacity (mM) and oxyhemoglobin saturation (%) measured in duplicate by an automated, direct-reading photometer (OSM-2; Radiometer, Copenhagen, Denmark). Blood samples were deproteinized with $ZnSO_4$ and $Ba(OH)_2$ for triplicate measurements of whole blood glucose concentration using glucose oxidase (Sigma Chemical Co., St. Louis, MO).

Calculations. The microsphere measurements of blood flow were by means of the reference withdrawal technique (6). Placental blood flow in each horn was the sum of individual cotyledonary blood flow in that horn. Endomyometrial blood flow for each horn was the sum of blood flows calculated for the five aliquots of endomyometrial homogenate multiplied by the ratio of the weight of the endomyometrium of that horn to the total weight of the five aliquots. Uterine blood flow (UBF) to the fetal horn (f) and the nonfetal horn (nf)

determined by microspheres (ms) ($UBF_{ms\text{-}f}$ and $UBF_{ms\text{-}nf}$, respectively) was calculated by adding placental and endomyometrial blood flows for each horn. Total uterine blood flow by the microsphere method ($UBF_{ms\text{-}T}$) was the sum of $UBF_{ms\text{-}f}$ and $UBF_{ms\text{-}nf}$.

The total transplacental diffusion rate of tritiated water (D^3H_2O) was calculated from the tritiated water fetal infusion rate after correction for fetal and placental ^3H_2O accumulation (3). This rate was used to calculate uterine blood flow by two different procedures. In the first procedure we made two separate calculations of total uterine blood flow (UBF_T) using the venoarterial concentration difference of tritiated water across the fetal $(^3H_2O)_{V\text{-}A}$ and nonfetal $(^3H_2O)_{\bar{V}\text{-}A}$ horn:

$$UBF_T = D^3H_2O/(^3H_2O)_{V\text{-}A} \quad (1)$$

and

$$UBF_T = D^3H_2O/(^3H_2O)_{\bar{V}\text{-}A} \quad (2)$$

This procedure assumes that the sampled venous concentration (V or $\bar{V}$) is representative of the venous concentration in the total uterine venous drainage (7). In the second procedure, uterine blood flows to the fetal (UBF_f) and nonfetal (UBF_{nf}) horn were calculated by solving two equations in which UBF_f and UBF_{nf} were the only unknown quantities:

$$D^3H_2O = UBF_f(^3H_2O)_{V\text{-}A} + UBF_{nf}(^3H_2O)_{\bar{V}\text{-}A} \quad (3)$$

and

$$(UBF_f/UBF_{nf}) = (PW_f/PW_{nf}) \quad (4)$$

where PW_f and PW_{nf} are the weights of placental cotyledons in the fetal and nonfetal horn, respectively. Equation 3 is the application of the Fick principle to the flux of tritiated water into the maternal circulation via the fetal and nonfetal horn. Equation 4 is based on the assumption that uterine blood flow per gram of placenta was equal in both horns. Evidence for the validity of this assumption is presented in Results.

Umbilical blood flow ($ml \cdot min^{-1}$) was calculated as the ratio: flux of tritiated water into the placenta via the umbilical circulation ($dpm \cdot min^{-1}$) divided by the arteriovenous concentration difference of tritiated water ($dpm \cdot ml^{-1}$) across the umbilical circulation (3). Substrate (oxygen and glucose) uptakes were calculated as the product of blood flow times the whole blood arteriovenous concentration difference of substrate.

Finally, the data on placental weight, microsphere counts in the uterine horns, blood oxygen, and tritiated water arteriovenous differences were used to compare the fraction of placental mass present in the fetal horn with the fraction of uterine blood flow, oxygen uptake, and tritiated water flux via the fetal horn:

Fraction of placental mass in fetal horn =

$$PW_f/(PW_f + PW_{nf}) \quad (5)$$

Fraction of total uterine blood flow via the fetal horn

$$= M_f/(M_f + M_{nf}) \quad (6)$$

where M_f and M_{nf} are the microsphere counts present in the fetal and nonfetal horn, respectively.

Fraction of total oxygen uptake via the fetal horn =

$$\{[M_f(O_2)_{A\text{-}V}]/[M_f(O_2)_{A\text{-}V} + M_{nf}(O_2)_{\bar{V}\text{-}A}]\} \quad (7)$$

where $(O_2)_{A\text{-}V}$ and $(O_2)_{\bar{V}\text{-}A}$ are the O_2 content arteriovenous differences across the fetal and nonfetal horn, respectively.

Fraction of tritiated water flux via the fetal horn =

$$\{[M_f(^3H_2O)_{A\text{-}V}]/[M_f(^3H_2O)_{A\text{-}V} + M_{nf}(^3H_2O)_{\bar{V}\text{-}A}]\} \quad (8)$$

Results

A total of seven uterine blood flow and uptake measurements was completed. Because the umbilical catheters in Animal 5 did not function, data were obtained across the umbilical circulation in six fetuses only. Fetal weight, gestational age, and weights of the placenta and endomyometrium composing the fetal horn and nonfetal horn are presented in Table I. The mean values of fetal weight, gestational age, and total endomyometrium weight were comparable to previously published values from our laboratory (3); however, the mean weight of placental cotyledons in the present study (369 ± 85 g) was less than that observed in an earlier report (486 ± 22 g) (3). Endomyometrial weight was consistently higher in the fetal horn. In six of the seven fetuses, the fetal horn contained more cotyledons and a greater placental mass.

Umbilical Blood Flow and Uptakes. Individual values for umbilical blood flow and fetal uptake of oxygen and glucose via the umbilical circulation are presented in Table II. Mean umbilical blood flow and oxygen consumption rate per kilogram of fetus were not significantly different from previously published values (3). However, fetal glucose uptake per kilogram of fetus (26.4 ± 4.0 vs 52.3 ± 7.2 $\mu mol \cdot min^{-1} \cdot kg^{-1}$) and the fetal glucose/oxygen quotient (0.38 ± 0.04 vs 0.68 ± 0.08) were significantly smaller ($P < 0.01$). These differences may be related in part to the difference in placental weights since umbilical glucose uptakes per kilogram of placental weight were not significantly different in the two studies (17.5 ± 3.6 vs 23.6 ± 2.4 $\mu mol \cdot min^{-1} kg^{-1}$, $P > 0.1$).

Uterine Blood Flow and Uptakes: Microsphere Method. In both horns, myoendometrial blood flow was a relatively small percentage (18 ± 1.5%) of uterine blood flow. Individual values for uterine blood flow and uptake of oxygen and glucose via the fetal and

Table I. Maternal Hemoglobin Type, Gestational Age, Fetal, Placental, and Endomyometrial Weights, and Number of Placental Cotyledons in Fetal Horn and Nonfetal Horn

Animal	HB Type	Gestational age (days)	Fetal weight (g)	Fetal horn			Nonfetal horn		
				Placenta (g)	Cotyledons (*n*)	Endomyometrium (g)	Placenta (g)	Cotyledons (*n*)	Endomyometrium (g)
1	AA	79	316	256	38	99	131	34	67
2	BB	76	259	195	41	131	237	46	123
3	AB	76	224	152	39	121	83	29	112
4	BB	77	224	255	49	112	114	39	69
5	AB	74	197	247	43	133	187	34	83
6	BB	75	160	208	50	104	151	33	81
7	AB	75	174	228	53	90	139	35	53
Mean		76	222	220	45	113	149	36	84
±SE		0.6	20	14	2	6	19	2	9

Table II. Umbilical Blood Flow and Uptake of Oxygen and Glucose[a]

Animal	Umbilical blood flow		Umbilical oxygen uptake		Umbilical glucose uptake	
	$ml \cdot min^{-1}$	$ml \cdot min^{-1}kg^{-1}$	$\mu m \cdot min^{-1}$	$\mu m \cdot min^{-1}kg^{-1}$	$\mu m \cdot min^{-1}$	$\mu m \cdot min^{-1}kg^{-1}$
1	83	263	120	380	11.0	34.8
2	66	255	107	413	3.5	13.5
3	85	379	101	451	5.7	25.4
4	95	424	119	531	8.1	36.2
5	—	—	—	—	—	—
6	93	581	71	444	5.2	32.5
7	64	368	50	287	2.8	16.1
Mean	81	378	95	418	6.1	26.4
±SE	5	49	12	33	1.2	4.0

[a] Blood flow and substrates uptakes are expressed per kilogram of fetal wet weight.

Table III. Uterine Blood Flows and Oxygen and Glucose Uptakes Calculated on the Basis of the Microsphere Data

Animal	Fetal horn			Nonfetal horn			Total		
	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)
1	343	340	59	187	170	27	530	510	86
2	314	230	34	273	281	48	587	511	82
3	303	376	46	158	217	25	461	593	71
4	307	340	36	149	162	18	456	502	54
5	367	284	29	254	227	29	621	511	58
6	163	222	23	116	165	18	279	387	41
7	256	197	33	147	121	24	403	318	57
$\bar{X}$	293	284	37	183	192	27	477	476	64
SEM	25	26	5	22	20	4	44	35	6

nonfetal horn are presented in Table III. The partitioning of total uterine blood flow and oxygen uptake between the fetal and nonfetal horn was strongly correlated with the partitioning of placental mass between the two horns (Table IV).

Uterine Blood Flow and Uptakes: Tritiated Water Method. The measurements of uterine arteriovenous concentrations differences of tritiated water, oxygen, and glucose across the fetal and nonfetal horns allowed two sets of calculations of total uterine blood flow (Equations 1 and 2) and uptakes for each experiment. The two sets are presented in Table V and show that in some experiments there was an appreciable discrepancy between estimates. This information indicated the need for a more precise calculation of total uterine blood by the tritiated water method that would take into account

Table IV. Fetal Horn Placental Weight (PW), Microsphere Uterine Blood Flow (UBF_{ms}), Uterine Oxygen Uptake ($\dot{V}O_2$), and Transplacental Tritiated Water Diffusion Rate (D^3H_2O), Expressed as Percentage of the Total for Both Horns

Animal	PW/PW_T (%)	$UBF_{ms\text{-}f}/UBF_{ms\text{-}T}$ (%)	$(\dot{V}O_2)_f/(\dot{V}O_2)_T$ (%)	$D^3H_2O/D^3H_2O_T$ (%)
1	66.1	64.8	66.7	66.7
2	45.2	53.5	45.0	57.9
3	64.6	65.7	63.4	65.6
4	69.2	67.4	67.7	74.7
5	56.9	59.1	55.6	56.2
6	57.9	58.4	57.4	53.7
7	62.2	63.4	61.9	64.7
$\bar{X}$	60.3	61.8	59.7	62.8
Correlation coefficient[a]	1.000	0.975	0.996	0.750

[a] Correlation with respect to the PW/PW_T variable.

Table V. Total Uterine Blood Flow and Oxygen and Glucose Uptakes Calculated on the Basis of Arteriovenous Differences of Tritiated Water, Oxygen, and Glucose Measured Across the Fetal (A-V) and Nonfetal (A-$\bar{V}$) Horns

Animal	(A-V Data)			(A-$\bar{V}$) Data		
	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)
1	577	571	99	630	573	90
2	520	380	57	623	642	110
3	313	388	47	312	427	50
4	372	413	44	529	578	63
5	717	555	56	637	570	72
6	263	358	38	218	309	34
7	458	354	59	486	399	80
$\bar{X}$	460	431	57	491	500	71
SEM	60	35	8	63	46	10

the different contributions of the fetal and nonfetal horns to total uterine blood flow.

Since it was apparent from the microsphere data that the uterine horn with the largest placental mass made the largest contribution to total uterine blood flow (Table IV), we assumed the fetal/nonfetal horn blood flow and placental mass ratios to be equal and calculated tritiated water blood flows separately for the two horns on the basis of this assumption (Equations 3 and 4 in Materials and Methods). Each blood flow was then used to calculate substrate uptakes. The results of these calculations are presented in Table VI. The comparison of Table III and Table VI data shows good agreement in the estimates of blood flow and uptakes by the microsphere and tritiated water method.

Discussion

Application of the Fick principle to the steady-state transplacental diffusion of highly diffusible molecules (e.g., tritiated water, ethanol, antipyrine) infused at a constant rate into the fetus is useful for metabolic studies of the pregnant uterus because it permits simultaneous determination of uterine and umbilical blood flows and substrate uptakes. However, application of the Fick principle to the uterine circulation is complicated by the absence of a common uterine vein representative of venous drainage from the entire uterus. To study this problem in the mid-gestation pregnant ewe, we placed catheters in both major uterine veins of ewes carrying a single fetus and sampled the effluents from both uterine horns during the fetal infusion of tritiated water. Uterine blood flow and substrate uptakes were calculated using the arteriovenous concentration differences of ^3H_2O and substrate across each horn separately. These calculations were compared with analogous calculations based on measurements of uterine blood by the radioactive microsphere method.

The two methods gave similar results. Mean total uterine blood flow in the seven ewes was 468 ± 60 ml/min by the tritiated water method and 477 ± 44 ml/min by the microsphere method. The total uterine blood flow was not significantly different from that measured by Rosenfeld *et al.* (8) in fetuses ranging from 57 to 85 days of gestation. However, the endomyometrial flow was a larger fraction of the total in the earlier

Table VI. Uterine Blood Flows and Oxygen and Glucose Uptakes Calculated on the Basis of the Tritiated Water Data[a]

Animal	Fetal horn			Nonfetal horn			Total		
	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)	Blood flow ($ml \cdot min^{-1}$)	Oxygen uptake ($\mu mol \cdot min^{-1}$)	Glucose uptake ($\mu mol \cdot min^{-1}$)
1	393	389	67	201	182	29	594	571	96
2	259	190	28	313	321	55	572	511	83
3	202	250	30	111	152	18	313	402	48
4	283	313	33	126	137	15	409	450	48
5	388	299	30	293	261	33	681	560	63
6	140	190	20	102	145	16	242	335	36
7	291	224	37	177	145	29	468	369	66
$\bar{X}$	279	265	35	189	192	28	468	457	63
SEM	35	28	6	32	27	5	60	35	8

[a] Blood flow calculations were based on Equations 3 and 4.

study (37 ± 2.7% vs 18 ± 1.5%), a difference possibly related to techniques used to separate placental from endomyometrial tissues. Total uterine substrate uptake measurements calculated by the two methods were also similar: 457 ± 35 vs 476 ± 35 μmol of oxygen/min and 63 ± 8 vs 64 ± 6 μmol of glucose/min.

In the final calculation of uterine blood flow and substrate uptakes by the tritiated water method, we took into consideration the partitioning of placental weight between the two uterine horns since the distribution of microspheres in the pregnant uterus showed that blood flow and placental mass partitioning were well correlated (Table IV). This refinement in total uterine blood flow and substrate uptake calculations appears to be more important in mid than in late gestation. Simultaneous sampling of the fetal and nonfetal horn uterine veins in late gestation ewes demonstrated that in most cases the two veins had similar concentrations of the blood flow indicator molecule (9). Furthermore, when there was an appreciable discrepancy, the side of the uterus with the smaller venoarterial difference of the flow indicator had also the smaller arteriovenous difference of oxygen so that the calculation of fetal oxygen uptake could be made fairly accurately without knowledge of blood flow distribution in the two horns (9). In the present study, however, the partitioning of tritiated water excretion between the two uterine horns was not precisely related to the partitioning of oxygen uptake (Table IV). Note that the distribution of tritiated water excretion via the fetal and nonfetal horns was likely to reflect umbilical blood flow distribution because transplacental diffusion of tritiated water is primarily blood flow limited (1). The umbilical/uterine blood flow ratio was quite small (0.2 ± 0.04), thus making umbilical blood flow the limiting factor in the placental clearance of the flow indicator. It is not surprising that umbilical blood flow and uterine oxygen uptake distribution were not well correlated at mid-gestation since the umbilical circulation received only a small fraction of the uterine oxygen uptake. The comparison of oxygen uptakes via the uterine and umbilical circulations shows that approximately 20% of the oxygen taken by the pregnant uterus was delivered to the fetus. The rest was metabolized by the uteroplacental mass at the rate of 345 ± 28 μmol/min. Further data analysis points to the placental cotyledons as the major site of uteroplacental oxygen consumption since the partitioning of placental mass and oxygen uptake between the two uterine horns were strongly correlated (Table IV).

The comparison of late gestation with mid-gestation data demonstrates important metabolic and circulatory developmental changes. The following comparison is with recent data on 16 near-term ewes, each carrying a single fetus (10). Eight of these ewes were homozygous for hemoglobin A and eight for hemoglobin B. From 76 to 132 days of gestation, fetal oxygen uptake increases from 95 to 1040 μmol/min, an 11-fold increase, whereas uteroplacental oxygen consumption increases approximately from 346 to 590 μmol/min, a less than 2-fold increase. As a consequence of the moderate increase in uteroplacental oxygen demand, the relative increase in oxygen uptake by the whole pregnant uterus is much less rapid than the increase in fetal uptake (3.5- vs 11-fold). These disproportionate changes in uteroplacental and fetal oxygen demands explain in part why uterine and umbilical blood flow have different relative growth rates in the second half of pregnancy. From 76 to 132 days of gestation, umbilical blood flow grows approximately from 80 to 600 ml/min, a 7.5-fold increase. By contrast, the growth of uterine blood flow is from 470 to about 1250 ml/min, a 2.7-fold increase. A similar difference in rates of increase of uterine and umbilical blood flows has been observed in bovine pregnancy (11). Clearly, the growth of uterine blood flow from mid-gestation to

term is related to the growth in metabolic demands of placenta plus fetus, whereas the growth of umbilical blood flow is related to the growth in fetal metabolic demands. The high O_2 requirements of the placenta at mid-gestation does not fit well the assumption that placental energy metabolism is primarily a function of the transport of nutrients to the fetus. If this were the case, one would expect placental O_2 to grow in proportion to fetal metabolic requirements. The data suggest that a large fraction of placental O_2 consumption is devoted to functions other than nutrient transfer from mother to fetus.

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