Movement of Oxygen, Glucose, and Lactate across the Uterus of the Awake Near-Term Guinea Pig

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ABSTRACT. In this study the uterine movement of oxygen, glucose, and lactate was quantitated in the awake late pregnant guinea pig. Mean uterine uptake of oxygen per kg of uterus with conceptus was $581 \mu\text{mol min}^{-1}$, which is comparable to the value reported for the awake near-term rabbit, but 30% higher than the value reported for the awake near-term sheep. Experiment-related anemia in some animals was associated with a reduced uterine oxygen uptake. The arteriovenous oxygen difference across the uterus correlated positively with the arterial oxygen content and the hemoglobin concentration and negatively with uteroplacental blood flow. Uterine oxygen uptake showed a positive correlation with both the arterial hemoglobin and the uteroplacental blood flow. Uterine lactate output accounted for 20% of uterine glucose uptake, assuming maternally derived glucose to be the only source for uterine lactate output. After correction for this lactate output, the uterine glucose uptake was $96.5 \mu\text{mol min}^{-1} \cdot \text{kg}^{-1}$ of pregnant uterus. This value is 30% higher than in the awake near-term rabbit and more than twice as high as that in the awake near-term sheep. Nevertheless, because of the high uterine demand for substrates, this uterine glucose uptake could only cover 45% of the caloric requirements of the pregnant uterus. The late pregnant guinea pig fetus may derive as much as 55% of its caloric uptake for fat deposition and protein accretion. Therefore, it is likely that the nonglucose uterine caloric uptake in the late pregnant guinea pig consists predominantly of fat precursors and amino acids. (*Pediatr Res* 20: 730-734, 1986)

Abbreviations

UBF, uteroplacental blood flow
IVC, inferior vena cava
Hb, hemoglobin
UW, uterine weight

The fetuses of the late pregnant guinea pig grow at a rate of 7% per day and total fetal weight can reach 50% of maternal prepregnant weight (1). This exceptional characteristic of guinea pig pregnancy implies a great influx of O_2 and nutrients into the pregnant uterus during the near-term period and makes this

species an interesting model for the study of fetal nutrition. However, quantitative data on the movement of O_2 and substrates across the uterus of the late pregnant animal can only be derived indirectly from separate studies on the UBF (2, 3) and on mean concentration gradients of various metabolic substrates across the pregnant uterus (4, 5). No combined data on UBF and concentration gradients across the uterus obtained in the same animal are available for this species. Therefore, the present study was designed to quantitate the uterine uptake of oxygen and glucose, and the uterine output of lactate in the awake pregnant guinea pig.

MATERIALS AND METHODS

Nineteen pregnant albino guinea pigs bred in our laboratory facility were used in this study. Dated pregnancies were obtained by using the technique of postpartum breeding (5). The animals were kept in individual cages in a controlled environment (19°C , 50% humidity) with a 13/11 h light/dark cycle, from the 30th day of pregnancy until after completion of the experiments. They were fed commercial guinea pig pellets,¹ hay, and water *ad libitum*. Their daily weight gain and food intake was comparable to values reported previously (6). Vitamin C was added to the drinking water twice a week, and vitamin E once weekly.

Surgical techniques. Between 44 and 50 days gestation, polyethylene catheters were inserted into the left ventricle of the heart, the abdominal aorta and the IVC using aseptic techniques (3, 5). The catheters were tunneled subcutaneously and exteriorized between the shoulder blades. They were flushed once weekly with saline. Experiments were performed after complete recovery of the daily weight gain, which was usually on the 4th or 5th day after surgery. The gestational age at the time of the experiment ranged from 50 to 60 days (median 57 days). On the day before the experiment, a small polyvinyl catheter was advanced under fluoroscopic control, through the IVC catheter into one of the ovarian veins (5, 7). An arterial blood sample was obtained at this time to determine the Hb concentration.

Experimental protocol. Three sets of arterial and venous blood samples were collected with an interval of 15 to 30 min between 1000 and 1200 h. The total volume of blood withdrawn was approximately 3.5 ml. After blood sampling, UBF was determined using $15 \mu\text{m}$ radioactive microspheres (NEN, Dreieich, West Germany), as described previously (3). Arterial blood pressure and heart rate were monitored continuously throughout the experiment, including the period of blood sampling and microsphere injection. Microspheres were injected only after stable readings for arterial blood pressure and heart rate had been

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¹ Composition of Hope Farms guinea pig pellets (LC23-B): carbohydrates (including 13% fibers): 66%, protein: 23%, fat: 4%, minerals: 6%. Gross energy: 4.5 kcal/g.

obtained for at least 15 min. Starting 15 s before and continuing until 30 s after the injection, a reference sample of blood was withdrawn at a constant rate ($0.9 \text{ ml} \cdot \text{min}^{-1}$) from the abdominal aorta. Two separate blood flow measurements were performed about 30 min apart. Some animals moved during one of the two microspheres injections or showed signs of stress reflected in an increase in blood pressure (> 5 torr), an increase in heart rate (> 20 beat per minute), and/or hyperventilation ($\text{PCO}_2 < 25$ torr). These measurements were discarded. In the other animals only the measurement with the best correlation between the flows to various organ pairs (indicative of better mixing of microspheres) was used in the subsequent analysis. The difference between the blood flows to paired organs never exceeded 10%.

After the second blood flow measurement, unimpaired venous outflow from the catheterized ovarian vein was verified fluoroscopically using a small bolus of contrast medium (7). After fluoroscopy, the animals were sacrificed with an overdose of pentobarbital sodium. The catheter positions were checked at autopsy, and all organs were dissected. In all animals, the tip of the catheter used for injection of microspheres appeared to be located in a satisfactory position in the left ventricle. The tip of the abdominal catheter was located between the kidneys and the aortic bifurcation. The tip of the ovarian vein catheter was always between 1 and 3 cm inside one of the ovarian veins.

Radioactivity in each tissue aliquot and in the reference samples was determined with a well scintillation counter adapted with a 3-inch crystal (Packard Autogamma Scintillation Counter 5220). The data were analyzed with a set of computer programs developed for processing data generated during microsphere experiments (8). All uterine, placental, and reference samples contained at least 700 microspheres.

Concentrations of glucose and lactate were determined with standard enzymatic techniques after perchloric acid precipitation (9). The hematocrit was determined in duplicate using the microcapillary technique. The Hb concentration and O_2 saturation were determined with the OSM2-apparatus (Radiometer, Copenhagen, Denmark) and arterial blood gases and pH with an ABL3 apparatus (Radiometer). The O_2 content was calculated

from the Hb, the O_2 saturation and the PO_2 as described previously (5).

Data presentation and statistics. No significant differences could be demonstrated between paired first, second, and third values of O_2 , glucose, and lactate (paired Student's *t* test). Therefore, the mean values for the three arterial and venous concentrations were used for statistical evaluation. The uterine uptakes in the present study were calculated based on the data from one uterine horn using the Fick principle. The obtained values were assumed to be representative for the whole uterus. The experimental data of anemic animals were compared with those of nonanemic animals using the unpaired Student's *t* test. Using Spearman's nonparametric correlation test, the interrelations were evaluated between the three arteriovenous concentration differences and the weight-specific UBF, between the three arterial concentrations and the related arteriovenous concentration differences, and in between the three arteriovenous concentration differences. The relationships between the UBF and the UW and between the arteriovenous O_2 difference and the UBF were quantitated with linear regression analysis. Throughout the text data will be presented as means $\pm$ SD.

RESULTS

Twelve of the 19 animals had an arterial Hb of more than 5.4 mM, which is the lower limit of the normal range (5). Some characteristics and experimental data obtained in the 12 nonanemic and the seven anemic animals are listed in Table 1. In the anemic as compared with the nonanemic group the arterial lactate concentration was significantly elevated and uterine O_2 uptake was significantly reduced. In the nonanemic animals the mean glucose/ O_2 and lactate/ O_2 quotients across the uterus were 1.23 ± 0.36 and -0.26 ± 0.08 , respectively. A decreased lactate/ O_2 quotient across the uterus most likely reflects increased anaerobic metabolism of the conceptus. Figure 1 illustrates the relationship between this quotient and the weight-specific uterine O_2 uptake for nine of 12 nonanemic animals in which both measurements were successfully performed and in all seven

Table 1. Characteristics and experimental data of all pregnant animals studied (mean $\pm$ SD and range)

	Nonanemic group (<i>n</i> = 12)		Anemic group (<i>n</i> = 7)*	
Characteristics				
Maternal wt (g)	1013 $\pm$ 103	884–1193	1048 $\pm$ 182	834–1323
Fetal wt (g)	206 $\pm$ 59	81–312	220 $\pm$ 67	129–320
Litter size	3.7 $\pm$ 1.3	2–7	3.9 $\pm$ 1.1	3–5
Arterial parameters				
Hematocrit (vol%)	33.5 $\pm$ 3.6	29–40	26.0 $\pm$ 2.5†	23–29
Hb (mM)	6.5 $\pm$ 0.9	5.4–7.9	4.6 $\pm$ 0.6†	3.8–5.2
Glucose (mM)	4.77 $\pm$ 0.57	3.89–5.83	4.72 $\pm$ 0.82	3.48–6.13
Lactate (mM)	1.20 $\pm$ 0.41	0.61–1.84	2.79 $\pm$ 1.98‡	0.82–6.62
Data from sampled horn				
Total wt (g)	143 $\pm$ 60	50–259	169 $\pm$ 45	101–227
Fetal no.	2.2 $\pm$ 0.9	1–4	2.6 $\pm$ 0.8	2–4
Fetal wt (g)	122 $\pm$ 54	40–233	147 $\pm$ 40	87–199
Placental wt (g)	10.6 $\pm$ 4.0	4.5 $\pm$ 16.1	11.2 $\pm$ 4.0	6.8–16.7
UBF (ml/min/kg·horn)	143 $\pm$ 37	83–194	124 $\pm$ 35	82–167
(Arteriovenous) O_2 (mM)	4.18 $\pm$ 0.69	3.06–5.18	3.38 $\pm$ 0.63‡	2.72–4.20
(Arteriovenous) glucose (mM)§	0.94 $\pm$ 0.28	0.43–1.41	0.66 $\pm$ 0.37	0.03–1.26
(v-a) lactate (mM)§	0.39 $\pm$ 0.11	0.29–0.59	1.00 $\pm$ 0.98	0.16–2.64
Oxygen uptake	581 $\pm$ 114	431–770	410 $\pm$ 116†	274–635
Glucose uptake§	122 $\pm$ 41	58–181	76 $\pm$ 48	5–162
Lactate output§,	51 $\pm$ 15	29–80	110 $\pm$ 113	26–340

* Arterial Hb < 5.4 mM.

† Significant difference between groups I and II ($p < 0.01$).

‡ Significant difference between groups I and II ($p < 0.05$).

§ Nine observations.

|| Expressed in $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ of the pregnant uterus.

Fig. 1. Relationship between the lactate/ O_2 quotient across the uterus and the uterine O_2 uptake. Nonanemic animals are represented by open circles, whereas the seven anemic animals are represented by filled circles. Note the decreased quotient when the uterine O_2 uptake is less than 350–400 $\mu\text{mol}/\text{min}/\text{kg}$ (uterus + conceptus).

anemic animals. Less than approximately 400 μmol of O_2 uptake, the lactate/ O_2 quotient appeared to fall progressively. Only the data obtained in the 12 nonanemic animals were used for the subsequent statistical analysis. The arteriovenous concentration differences of O_2 , glucose, and lactate did not correlate with the total weight of the uterine horn. On the other hand, the UBF varied as a function of UW ($\text{UBF} = 0.12 \text{ UW} + 2.82$, $r = 0.84$, $p < 0.001$). Therefore, the movement of O_2 , glucose, and lactate across the uterus varied in proportion to the UBF. The total weight of the sampled uterine horn did not correlate with gestational age due to the variation in the number of fetuses.

Evaluation of the relationships between the three arteriovenous concentration gradients and the UBF showed only a significant negative correlation between the arteriovenous O_2 difference and the UBF (Spearman $r = -0.68$; $p < 0.01$). This relationship was quantitated with linear regression (Fig. 2). The arteriovenous O_2 difference correlated positively with the arterial O_2 content (Spearman $r = 0.51$, $p < 0.05$) and with the arterial Hb (Spearman $r = 0.48$, $p < 0.05$). The arteriovenous glucose and lactate differences across the uterus did not correlate with their arterial concentration. Finally, the three arteriovenous concentration gradients were not interrelated.

DISCUSSION

An important finding in this study is the significantly lower uterine O_2 uptake in the anemic as compared with the nonanemic guinea pig without demonstrable interference with pregnancy. The reduced uterine O_2 uptake in anemia is caused by the lower arteriovenous O_2 difference across the uterus without a significant change in UBF. It is possible that the UBF in a state of anemia can not be increased because of the limited cardiovascular reserves in the late pregnant guinea pig (3). In four of the seven anemic animals uterine O_2 uptake was less than 400 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ of pregnant uterus (Fig. 1). In these animals, the concomitant lactate/ O_2 quotient across the uterus was significantly lower than the mean value for nonanemic animals (Table 1). These data suggest that the lower limit of the normal range of uterine O_2 uptake is approximately 400 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ of pregnant uterus.

Values for UBF, arterial O_2 , glucose, and lactate concentrations, the related arteriovenous concentration gradients and the glucose/ O_2 quotient across the uterus in the 12 nonanemic animals are comparable with previous observations in our laboratory (3, 5). The relationship between UBF and UW found in this study is almost identical to that reported previously (3). The

Fig. 2. Relationship between the arteriovenous O_2 difference across the uterus and the weight-specific UBF. Linear regression analysis resulted in the equation: arteriovenous $O_2 = 6.20 - 0.014 \text{ UBF}$ ($r = -0.76$, $p < 0.005$).

uterine O_2 uptake in the present study ranges from 431 to 770 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ of the pregnant uterus (Table 1). This relatively large variation may be largely attributed to the methods used: the measurement of UBF as well as that of the arteriovenous O_2 difference is associated with a coefficient of variation of 10–15% (3, 5). Multiplication of these two variables to calculate uptake magnifies these errors to 20–30%. The mean value for uterine O_2 uptake in this study is 581 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (uterus + conceptus). This value is higher than the approximately 400 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ reported previously for the near-term guinea pig (10). However, the latter observations were made only 2 h after surgery and anesthesia, when uteroplacental and fetal metabolism may still be suppressed (11, 12).

The negative relationship between the arteriovenous O_2 difference and UBF decreases the dependence of the uterine O_2 uptake of the two contributing variables. In the present study UBF varied between approximately 80 and 200 $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (uterus + conceptus) (Table 1). Despite the observed negative correlation between UBF and arteriovenous O_2 difference across the uterus (Fig. 2), uterine O_2 uptake varies in proportion to both UBF and arteriovenous O_2 difference. The insufficient compensatory in-

crease in the arteriovenous O_2 gradient across the uterus in response to a fall in UBF may well be a consequence of the relatively high uterine O_2 extraction of approximately 65% in this species in the late pregnancy (5). At normal UBF rates, the uterus of the late pregnant guinea pig extracts three times as much O_2 than does the ewe of corresponding gestational age (13). This so-called "efficiency of uterine O_2 uptake" (14) may explain why the guinea pig is able to accommodate such a large conceptus. The mean uterine O_2 uptake in this study is about 50% higher than strictly needed for uterine oxidative requirements. The "excess" O_2 uptake may be used by the fetus for nonvital purposes such as bodily movements and tissue growth. In the presence of a compromised UBF, both functions can be curtailed to protect basal energy metabolism.

The values of uterine O_2 uptake obtained in the present study are similar to those reported for the awake near-term rabbit (approximately $530 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) (15) and about 30% higher than those observed in the awake late pregnant sheep (12) and cow (16). The fractional distribution of the uterine O_2 uptake between uteroplacental and fetal tissue can only be determined when the O_2 uptake of one of these two tissues is known. Values reported from *in vitro* measurements of placental O_2 uptake in the sheep, rabbit, rat, mouse, guinea pig, and man range from 100 – $500 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (17–20). However, an *in vivo* study in the near-term ewe demonstrated the importance of intact uteroplacental and umbilical circulations as well as the absence of anesthesia for normal uteroplacental O_2 consumption (12). In the latter study the uteroplacental O_2 uptake, measured in the awake near-term ewe with intact uterine and umbilical circulations, amounted to $980 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. If the *in vivo* weight-specific uteroplacental O_2 uptake in the near-term guinea pig is assumed to be as high as in the near-term ewe, the fetal O_2 uptake can be estimated from the value for the uterine O_2 uptake. In the present study, uterine weight consisted for 85% of fetal mass and for 15% of uteroplacental tissue (Table 1). A mean uterine O_2 uptake of $581 \mu\text{mol}$ is then associated with a fetal O_2 uptake of approximately $511 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. An over- or underestimation of the weight-specific uteroplacental O_2 uptake by 20% would change the fetal value by only 7%. Therefore, this estimate may be accepted to be a close approximation of the actual fetal O_2 uptake. It is striking that it is 42% higher than the value of $360 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ reported for the near-term sheep (21). However, the near-term fetal guinea pig contains 76% water, less than the 83.3% of the fetal lamb of corresponding gestational age (1, 22). On the basis of these data a fetal O_2 uptake (expressed per kg of dry weight) of $2.1 \mu\text{mol}/\text{min}$ can be calculated for both species.

The reported value of total O_2 uptake of $600 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (23) in the adult guinea pig appears to be slightly higher than that estimated for fetal O_2 uptake. In contrast, fetal O_2 consumption per kg is clearly higher than that of the mother (24) in many larger animals. For instance, the late pregnant fetal lamb consumes twice as much O_2 per kg than the mother (360 versus $180 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$). It has been postulated that the low O_2 requirements of the fetus per unit of body weight as

compared to that of the mother enables the guinea pig to grow a conceptus that is relatively larger than that in the sheep for example (24).

In this study no relationship is observed between the arterial glucose concentration and the arteriovenous glucose gradient across the uterus. This observation is in contrast with previous observations obtained in comparable experimental conditions in various other species (25). A correlation between the arterial glucose concentration and the arteriovenous glucose difference may remain undetected because of the relatively small range of arterial glucose concentrations in this study (Table 1). The mean uterine glucose uptake in this study is $122 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. The uterine lactate output accounts for 20% of uterine glucose uptake, assuming no uterine lactate production from other sources. The "net" uterine glucose uptake, which is defined as the uterine glucose uptake after subtraction of the lactate output, amounts to $96.5 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ of pregnant uterus. In the near-term sheep (11) and rabbit (15) values for net uterine glucose uptake have been found to be 40 and $70 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ of pregnant uterus, respectively.

The caloric value of the guinea pig fetus has been determined at various points in gestation in a cross-sectional study using bomb calorimetry (1). Using the equations reported in that study the values for the daily fetal accretion of water, fat, protein, and non-fat and non-protein substances (glycogen, minerals, etc.) have been calculated for the 57 days pregnant guinea pig. In addition, the caloric equivalent of the fetal O_2 consumption was calculated using the estimated value derived from the data on uterine O_2 uptake in the present study. The results of these calculations are listed in Table 2. The net uterine glucose uptake in this study was $96.5 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ of pregnant uterus. The caloric equivalent of glucose equals $0.74 \text{ kcal} \cdot \text{mmol}^{-1}$. Consequently, the caloric equivalent of the net glucose uptake can be calculated to be $0.0965 \times 0.74 \times 1440 (\text{min}) = 102.8 \text{ kcal} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$ of pregnant uterus. This value represents 45% of the total fetal caloric requirements. Since the weight-specific uteroplacental glucose consumption is relatively large (12), it is likely that the uterine glucose uptake will cover less than 40% of the fetal caloric requirements. About 55% of the fetal caloric requirements are needed to generate new protein and fat (Table 2). The high caloric accretion in protein and fat may be accepted to have an important impact on fetal O_2 uptake. The energy costs for synthesis may range from 10% (fat) to 30% (protein) of the accreted caloric value (26), which corresponds with almost 30% of the fetal O_2 uptake. The high accretion rate in protein and fat is also likely to be associated with a large fractional uptake of amino acids and fat precursors by the pregnant uterus. The guinea pig placenta is readily permeable for free fatty acids (27). In addition, fat precursors of maternal origin contribute importantly to the lipids in the fetal tissues (28). Quantitation of the uterine uptake of fat precursors using the Fick principle may be difficult. The relatively large molecular weight of the most important fat precursors, the free fatty acids, will couple a small gradient across the uterus in μM (5) with a high transplacental transfer rate in grams. Also the amino acids are known to be

Table 2. Fetal metabolism and growth in 57 days pregnant guinea pig*

	O_2 uptake (mmol)	Tissue accretion (g)	Caloric equivalent (kcal)	Fraction of total caloric uptake (%)
Water		41.7	0	0
Fat		7.3	67.9	29.8
Protein		10.2	56.1	24.6
Other tissue		6.8	21.7	9.5
Total growth		66.0	145.7	63.9
O_2 †	735.84		80.7	35.6

* The growth of each type of fetal tissue is calculated on the basis of data reported by Sparks *et al.* (1). Values are expressed per kg of fetal weight and per day.

† Caloric equivalent of oxygen equals $109.7 \text{ kcal}/\text{mole}$ of O_2 (STP) (25).

easily transferred across the guinea pig placenta by an active carrier system (29). The question remains to be answered whether glucose serves primarily as a fuel for the oxidative metabolism, and fat precursors and amino acids as building stones for fetal growth. The metabolic fate of each nutrient within the uteroplacental compartment can only be determined in studies which involve the continuous infusion of labeled nutrients into the maternal circulation.

REFERENCES

1. Sparks JW, Girard J, Callikan S, Battaglia FC 1985 Growth of the fetal guinea pig: physical and chemical characteristics. *Am J Physiol* 248:E132-E139
2. Myers SA, Sparks JW, Makowski EL, Meschia G, Battaglia FC 1982 Relationship between placental blood flow and placental and fetal size in guinea pig. *Am J Physiol* 243:H404-H409
3. Peeters LLH, Grutters G, Martin CB 1980 The distribution of cardiac output in the unstressed pregnant guinea-pig. *Am J Obstet Gynecol* 138:1177-1184
4. Block SM, Sparks JW, Johnson RL, Battaglia FC 1985 Metabolic quotients of the gravid uterus of the chronically catheterized guinea pig. *Pediatr Res* 19:840-845
5. Peeters LLH, Mårtensson L, van Kreel BK, Wallenburg HCS 1984 Uterine arterial and venous concentrations of glucose, lactate, ketones, free fatty acids, and oxygen in the awake pregnant guinea pig. *Pediatr Res* 18:1172-1175
6. Sparks JW, Pegorier JP, Girard J, Battaglia FC 1981 Substrate concentration changes during pregnancy in the guinea pig studied under unstressed steady state condition. *Pediatr Res* 15:1340-1344
7. Peeters LLH, Mårtensson L, Gilbert M, Pénicaud L 1984 The pregnant guinea pig, rabbit and rat as unstressed catheterized models. In: *Animal Models in Fetal Medicine*, vol IV. Nathanielsz PW (ed) Perinatology Press Inc, Ithaca, NY, pp 77-108
8. Saxena PR, Schamhardt HC, Forsyth RP, Loeve J 1980 Computer programs for the radioactive microsphere technique. Determination of regional blood flows and other hemodynamic variables in different experimental conditions. *Comp Prog Biomed* 12:63-84
9. Bergmeyer HU (ed) 1974 *Methods of Enzymatic Analysis*, Vols 2-4. Academic Press Inc, New York
10. Moll W, Kunzel W, HG Ross 1970 Gas exchange of the pregnant uterus of anaesthetized and unanaesthetized guinea pigs. *Respir Physiol* 8:303-310
11. Battaglia FC, Meschia G 1981 Foetal and placental metabolism: their interrelationship and impact upon maternal metabolism. *Proc Nutr Soc* 40:99-113
12. Meschia G, Battaglia FC, Hay WH, Sparks JW 1980 Utilization of substrates by the ovine placenta. *Fed Proc* 39:245-249
13. Murray RD, Jones RO, Johnson R, Meschia G, Battaglia FC 1985 Uterine and whole body oxygen extractions in the pregnant rabbit under chronic steady-state conditions. *Am J Obstet Gynecol* 152:709-715
14. Bartels H 1970. In search of the "best" placenta. In: Bartels H (ed) *Prenatal Respiration*. North Holland, Amsterdam, pp 121-123
15. Johnson RL, Block SM, Gilbert M, Battaglia FC, Maschia G 1983 Uterine oxygen and substrate uptakes of the pregnant rabbit under chronic steady state conditions. *Proc Soc Gynecol Invest* 113:(abstr)
16. Comline RS, Silver M 1976 Some aspects of fetal and uteroplacental metabolism in cows with indwelling umbilical and uterine vascular catheters. *J Physiol (Lond)* 260:571-586
17. Campbell AGM, Dawes GS, Fishman AP, Hyman AI, James GB 1966 The oxygen consumption of the placenta and fetal membranes in the sheep. *J Physiol* 182:439-464
18. Carstensen MH, Leichtweiss HP, Schroeder H 1982 The metabolism of the isolated artificially perfused guinea pig placenta. I. Excretion of hydrogen ions, ammonia, carbon dioxide and lactate, and the consumption of oxygen and glucose. *J Perinat Med* 147:147-153
19. Raye JR, Killam AP, Battaglia FC, Makowski EL, Meschia G 1971 Uterine blood flow and O₂ consumption following fetal death in sheep. *Am J Obstet Gynecol* 111:917-924
20. Illsey NP, Penfold P, Bardsley SE, Tracey BM, Aarnoudse JG 1983 The effects of anoxia on human placental metabolism and fetal substrate profiles investigated by an in vitro placental perfusion technique. *Trophoblast Res* 1:55-70
21. Bell AW, Battaglia FC, Makowski EL, Meschia G 1985 Relationship between metabolic rate and body size in fetal life. *Biol Neonate* 47:120-123
22. Rattray PV, Garrett WN, East NE, Hinman N 1974 Growth, development and composition of the ovine conceptus and mammary gland during pregnancy. *J Animal Sci* 38:613-626
23. Morton M, Tsang H, Hohimer R, Ross D, Thornburg K, Faber J, Metcalfe J 1984 Left ventricular size, output, and structure during guinea pig pregnancy. *Am J Physiol* 246:R40-R48
24. Battaglia FC, Meschia G 1978 Principal substrates of fetal metabolism. *Physiol Rev* 58:499-527
25. Simmons MA, Battaglia FC, Meschia G 1979 Placental transfer of glucose. *J Dev Physiol* 1:227-243
26. van Es AJH 1980 Energy costs of protein deposition. In: Buttery PJ, Lindsay DB (eds) *Protein Deposition in Animals*. Butterworths, London, pp 215-224
27. Jones CT 1976 Lipid metabolism and mobilisation in the guinea pig during pregnancy. *Biochem J* 156:357-365
28. Thomas CR, Lowy C 1984 Contribution of circulating maternal lipids to fetal tissues in the guinea pig. *J Dev Physiol* 6:143-151
29. v Dijk JP, v Kreel BK 1978 Transport and accumulation of alpha-aminoisobutyric acid (A.I.B.) in the guinea pig placenta. *Pfluegers Arch* 377:217-224