Effect of Maternal Glucose Concentration on Uteroplacental Glucose Consumption and Transfer in Pregnant Sheep (42830)

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Abstract. **The present study was designed to measure the relationships between maternal arterial glucose concentration ($[\mathrm{Gl}]_A$) and fetal arterial glucose concentration ($[\mathrm{Gl}]_a$), uteroplacental glucose consumption (UPGC), and the rate of uteroplacental glucose transfer to the fetus (UPGT) in pregnant sheep in late gestation. $[\mathrm{Gl}]_A$ was controlled by a glucose clamp technique and the glucose flux rates of the uteroplacenta were quantified by the Fick principle. $[\mathrm{Gl}]_A$ varied from 1.81 to 154.7 mg/dl; $[\mathrm{Gl}]_a$ was directly related to $[\mathrm{Gl}]_A$: $[\mathrm{Gl}]_a = 0.374\ [\mathrm{Gl}]_A + 1.81$, $r = 0.873$, $P < 0.001$. Fetal arterial blood oxygen content decreased with $[\mathrm{Gl}]_A$ ($P < 0.05$) and fetal arterial blood lactate concentration increased with $[\mathrm{Gl}]_A$ ($P < 0.001$). There was no significant effect of $[\mathrm{Gl}]_A$ on the rates of uteroplacental lactate production, uteroplacental oxygen consumption, fetal oxygen consumption, or uterine or umbilical blood flow. Both UPGC and UPGT were directly related to $[\mathrm{Gl}]_A$: UPGC $= -2.221 \times 10^{-3}\ \chi^2 + 0.646 \times -6.016$, $r = 0.80$; UPGT $= -1.208 \times 10^{-3}\ \chi^2 + 0.405 \times -2.416$, $r = 0.90$. UPGC and UPGT were approximately parallel over the range of $[\mathrm{Gl}]_A$ studied (UPGC = 1.19 UPGT + 3.79, $r = 0.764$). These results demonstrate the importance of UPGC to maternal-fetal glucose homeostasis and indicate that factors regulating uteroplacental glucose consumption and transfer to the fetus become limiting at comparable levels of $[\mathrm{Gl}]_A$ and $[\mathrm{Gl}]_a$. The estimated kinetic constants for UPGC represent the metabolism of glucose by the uteroplacental tissues, but the estimated kinetic constants for UPGT represent the metabolism of glucose by the fetus as well as the transfer of glucose by the uteroplacenta to the fetus.**

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Net glucose consumption by the uteroplacental tissues in pregnant sheep is quite large, averaging about 37 mg/min (1). This rate of glucose consumption accounts for 50–70% of uterine glucose uptake at term (2) and as much as 90% at midgestation (3). The fates of glucose taken up by the uteroplacental tissues of sheep include oxidation, glycogen formation, and conversion to lactate and fructose (1, 4). Glycogen formation from glucose has not been quantified *in vivo*. Fructose production may account for about 0–3 mg/min (5) and lactate production for about 6-10 mg/min (6). The remainder of the glucose consumed by the uteroplacenta could, if fully oxidized, account for about two thirds of the oxygen consumed by these tissues (1). Uteroplacental glucose consumption also determines the concentration of glucose in the umbilical vein. For example, Simmons *et al.* (7) have calculated in term pregnant sheep that without uteroplacental glucose consumption umbilical arterial glucose concentration would rise from about 20 mg/dl to about 45 mg/dl.

Based on these observations, it is important to understand the mechanisms that regulate uteroplacental glucose consumption. However, there has been relatively little study of such regulation. In previous studies in sheep we quantified net glucose consumption in sheep in late gestation (2) and showed that the rate of uteroplacental glucose consumption was directly related to maternal arterial glucose concentration. This observation, however, was based on studying uteroplacental glucose consumption at only two concentrations of maternal arterial glucose.

The present study was conducted to measure glucose consumption by the uteroplacenta and to assess the regulation of this process by maternal glucose concentration. Experiments were conducted in late gestation pregnant sheep. Maternal arterial glucose concen-

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tration was controlled using a glucose clamp technique and net uteroplacental glucose uptake and transfer to the fetus were quantified using the Fick principle.

Materials and Methods

Animal Preparation. Ten pregnant Columbia-Rambouillet ewes, each carrying a single fetus, were studied between 130 and 142 days of gestation. The ewes were fasted for 2 days prior to surgery. Surgery was performed under intravenous pentobarbital sedation (5 mg/kg) and pontocaine spinal anesthesia (6 mg in hypertonic glucose). Maternal catheters for infusion were placed into a femoral vein through a groin incision. Maternal catheters for sampling included a femoral artery catheter (placed via the groin incision) and, after a midline laparotomy, a uterine venous catheter placed into the main uterine vein draining the pregnant uterine horn containing the study fetus. Using a standard hysterotomy approach, catheters for fetal infusions were placed in the fetal femoral veins via pedal veins. Catheters for fetal blood sampling were placed in the fetal abdominal aorta via a pedal artery and into the common umbilical vein. All catheters were tunneled subcutaneously through a flank incision on the ewe and kept within a plastic pouch attached to the ewe's skin. The catheters were flushed every other day with heparinized 0.9% w/v sodium chloride (30 units of heparin/ml of 0.9% sodium chloride). The ewes were allowed to recover from surgery for a least 5 days before study. They were kept in carts and given an *ad libitum* diet of alfalfa pellets, water, and mineral supplement. The sheep were kept in a room with the temperature controlled between 15 and 20°C. At least two sheep were always kept together for company. At the end of the study each animal was sacrificed with a rapid intravenous infusion of T-61 euthanasia solution (Taylor Pharmaceutical Co., Decatur, IL). The study was approved by the University of Colorado Health Sciences Center Institutional Animal Care and Use Committee.

Study Design. Each ewe was fasted for 24–48 hr prior to study to reduce blood glucose concentration. Each ewe was studied during a control period and during two glucose infusion periods, one with moderate levels of glycemia (40-90 mg/dl) and one with high levels of glycemia (>90 mg/dl). The control period lasted 150 min and the two glucose infusion periods each lasted 110 min.

Following the control period, glucose was infused intravenously into each ewe using a hyperglycemicc glucose clamp technique modified (8) from DeFronzo *et al.* (9) according to the equation:

$$Ginf(\text{new}) = Ginf(\text{previous}) \times Gd/Gi + \{[(Gd - Gi) \times 2 \times Wt]/10\ \text{min}\}$$

where $Ginf$ = glucose infusion rate in mg/min, Gi is maternal arterial blood glucose concentration at any time "i," Gd is the desired glucose concentration, "2" is the estimated glucose space in dl/kg body wt, "wt" is in kg, and "/10 min" converts the glucose pool correction (in braces) to an arbitrary rate of correction over 10 min. The initial $Ginf$ was 2.5 mg/min/kg based on other studies in our laboratory which demonstrated that this rate is about equal to basal glucose production rate for normoglycemic, late-gestation pregnant sheep (2). Maternal arterial blood glucose was measured in duplicate every 5 min and the average value entered into a programmed calculator that used the above equation, a constant for the infusion pump plus syringe (ml/min/setting), and the infusate glucose concentration (458 mg/ml) to calculate the new pump setting.

Blood Sampling, Chemical and Analytical Methods. Maternal arterial, uterine venous, umbilical venous, and fetal arterial blood samples were drawn simultaneously into plastic syringes lined with a mixture of EDTA and sodium fluoride. These samples were used for determination of glucose and antipyrine concentrations (total of 0.5 ml/catheter/sample) using chemical methods previously described (2, 10, 11). At the same time whole blood (200 μl) from each catheter was drawn into glass capillaries lined with dried heparin and sodium fluoride. The capillary samples were used for measurement of blood oxygen capacity and percentage of oxygen saturation using a Radiometer OSM-2 Hemoximeter in order to calculate blood oxygen content. These blood samples were drawn at 60, 100, 120, 130, 140, and 150 min of the control period and at 20, 40, 60, 80, 90, 100, and 110 min of each clamp period.

Maternal arterial blood glucose concentration for maintaining the glucose clamp was measured with a Yellow Springs Model 23A glucose analyzer on blood samples taken every 5 min from the maternal arterial catheter. The glucose analyzer was calibrated to an accuracy of ± 1.0 mg/dl. A standard with a concentration of glucose close to that in the blood was analyzed before each blood sample and used to keep the instrument calibrated throughout the study.

Fetal blood samples were replaced by equal volumes of maternal blood immediately after sampling.

Infusates. Glucose for maternal infusion consisted of 50% dextrose (w/v) in water (Travenol Laboratories, Inc., Deerfield, IL). The glucose concentration in this solution was measured at 458 mg/ml with the same standard glucose oxidase method used in blood. Antipyrine for infusion was prepared as a 10% solution in normal saline and was infused into a fetal vein at about 10 mg/min. Infusions were performed with Sage Model 355 continuously variable syringe infusion pumps precalibrated by syringe size to ml/min/setting.

Calculations. Umbilical blood flow was calculated by the steady-state diffusion technique using antipyrine (10). Net glucose, lactate, and oxygen uptakes by the uterus, the fetus (equal to the net transfer from uteroplacenta to fetus), and the uteroplacenta (equal to net uteroplacental consumption) were calculated by the Fick principle as previously described (1). Lactate production rate by the uteroplacenta was calculated as the sum of the net lactate uptake rates by the uterine and the umbilical circulations (1, 6). These calculations used the average blood flow and average arteriovenous substrate concentration differences during the last 30 min of each study period.

Statistics. Steady state was defined during each 30-min sampling period as less than a 5% variation of individual values around the period mean value with no consistent trend to increase or decrease. The sampling period mean value was used for intra- and inter-animal comparisons using paired *t* test and analysis of variance. Regression analysis used the standard least-squares method for linear correlations. Best-fit multiple linear correlations were made using a Sigma Plot 3 computer program.

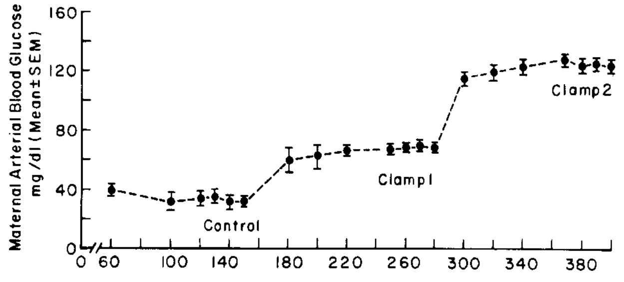

Figure 1. Maternal arterial blood glucose concentrations (mean ± SEM) are plotted at each sampling time during the three study periods.

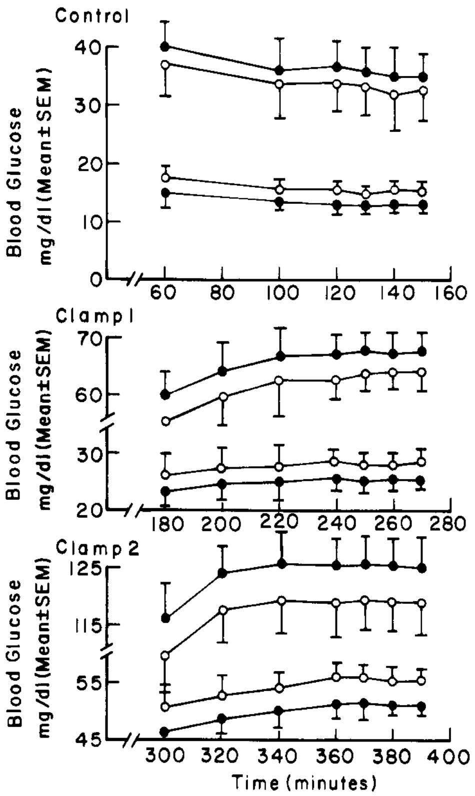

Figure 2. Maternal arterial and uterine venous (upper closed and open circles, respectively, in each panel), and fetal arterial and umbilical venous (lower closed and open circles, respectively, in each panel) blood glucose concentrations (mean ± SEM) are plotted at each sampling time during the three study periods. The constancy of the concentrations and the arteriovenous concentration differences demonstrate the presence of steady-state conditions for glucose.

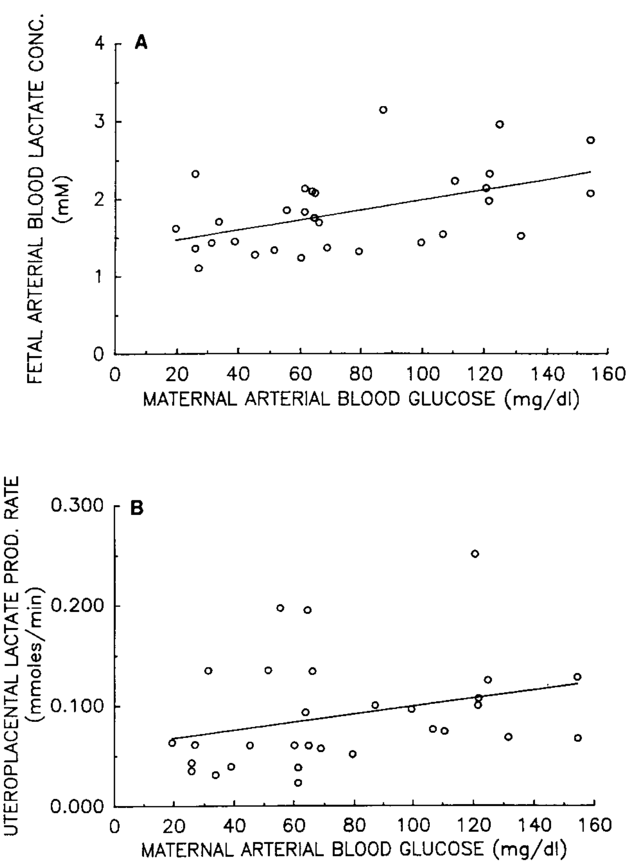

Figure 3. A, Fetal arterial blood lactate concentration ($[L]_a$) increased with maternal arterial blood glucose concentration ($[Gl]_a$): $[L]_a = 0.00654\,[Gl]_A + 1.34$, $r = 0.502$, $P < 0.001$. B, Uteroplacental lactate production rate (LPR) did not change significantly with $[Gl]_A$: $LPR = 0.000401\,[Gl]_A + 0.06$, $r = 0.296$, $P > 0.1$.

Results

Figure 1 presents the maternal arterial blood glucose concentrations ($[Gl]_A$) in the three study periods. Figure 2 presents the blood glucose concentrations in the three study periods in the maternal artery and uterine vein and in the fetal artery and umbilical vein. These data demonstrate that steady-state conditions for glucose concentrations in the uterine and umbilical circulations prevailed during each study period.

Mean (±SEM) values for measured substrate concentrations and flux rates during each study period are presented in Table 1. Fetal arterial blood lactate concentration ($[L]_a$) (Fig. 3A) increased with $[Gl]_A$ ($y = 0.00654x + 1.34$, $r = 0.502$, $P < 0.001$). There were no significant differences among the three study periods for maternal arterial blood lactate concentration ($[L]_A$), fetal or maternal lactate uptake rates, uteroplacental lactate production rate (LPR) (Fig. 3B), fetal or utero-

Table I. Substrate Concentrations and Flux Rates

	Mean (SEM)					
	A		B		C	
	Low glucose period		Medium glucose period		High glucose period	
Glucose Maternal arterial (mg/dl)	35.4	(3.6)	67.8[a]	(2.6)	125.4	(5.4)[a,b]
Glucose Fetal arterial (mg/dl)	13.7	(1.5)	25.8[a]	(1.6)	51.3	(2.5)[a,b]
Uterine glucose uptake (mg/min)	26.0	(3.7)	44.9[a]	(4.3)	70.4	(3.8)[a,b]
Fetal glucose uptake (mg/min)	10.4	(1.8)	19.4[a]	(1.2)	28.9	(1.5)[a,b]
Uteroplacental glucose uptake (mg/min)	15.6	(2.1)	24.3[a]	(3.2)	41.6	(3.1)[a,b]
Oxygen content Fetal arterial (m*M*)	4.14	(0.26)	3.82	(0.23)	3.49	(0.21)[a]
Oxygen content Maternal arterial (m*M*)	6.06	(0.13)	5.96	(0.07)	5.84	(0.09)[a]
Uterine oxygen uptake (mmol/min)	1.47	(0.12)	1.59	(0.13)	1.49	(0.15)
Fetal oxygen uptake (mmol/min)	0.81	(0.12)	0.87	(0.13)	0.86	(0.13)
Uteroplacental oxygen uptake (mmol/min)	0.658	(0.102)	0.715	(0.119)	0.629	(0.091)
Lactate Fetal arterial (m*M*)	1.567	(0.114)	1.886	(0.185)[a]	2.072	(0.168)[a]
Lactate Maternal arterial (m*M*)	1.010	(0.120)	0.899	(0.126)	1.073	(0.203)
Maternal lactate uptake (mmol/min)	0.032	(0.012)	0.028	(0.005)	0.040	(0.007)
Fetal lactate uptake (mmol/min)	0.048	(0.010)	0.053	(0.014)	0.070	(0.013)
Uteroplacental lactate production (mmol/min)	0.080	(0.017)	0.081	(0.015)	0.109	(0.016)
Uterine blood flow (ml/min)	952	(81)	985	(83)	949	(78)
Umbilical blood flow (ml/min)	593	(86)	594	(82)	573	(81)

[a] Different from low glucose period, $P < 0.05$.
[b] Different from medium glucose period, $P < 0.05$.

placental oxygen uptake rates, and uterine and umbilical blood flows. Fetal and maternal arterial blood oxygen contents (O_2a and O_2A, respectively) (Fig. 4) tended to decrease as maternal and fetal arterial blood glucose concentrations increased; the trend was significant for O_2a vs $[Gl]_A$ ($y = -0.00827x + 4.44$, $r = 0.411$, $P < 0.05$) but not for O_2A vs $[Gl]_A$ ($y = -0.00229 + 6.13$, $r = 0.27$, $P > 0.2$).

Fetal arterial blood glucose concentration ($[Gl]_a$) was directly related to maternal arterial blood glucose concentration ($[Gl]_A$) according to the equation: $[Gl]_a = 0.374\ [Gl]_A + 1.81$, $r = 0.87$, $p < 0.001$ (Fig. 5). Uterine glucose uptake rate (UtGU) (Fig. 6A), net uteroplacental glucose transfer (UPGT, equal to net fetal glucose uptake rate via the umbilical circulation) (Fig. 6B), and net uteroplacental glucose uptake (consumption or UPGC) (Fig. 6C) were directly related to maternal arterial blood glucose according to the equations:

$$\text{UtGU} = -0.0035\ ([Gl]_A)^2 + 2.062\ [Gl]_A - 8.021,\ r = 0.86 \qquad \text{[Eq. 1]}$$

standard errors of the estimate: 0.0015 for the $([Gl]_A)^2$ term, 0.255 for the $[Gl]_A$ term, 9.403 for the y-intercept.

$$\text{UPGT} = -0.0012\ ([Gl]_A)_2 + 0.405\ [Gl]_A - 2.416,\ r = 0.90 \qquad \text{[Eq. 2]}$$

standard errors of the estimate: 0.0005 for the $([Gl]_A)^2$ term, 0.091 for the $[Gl]_A$ term, 3.348 for the intercept.

$$\text{UPGC} = -0.0022\ ([Gl]_A)^2 + 0.646\ [Gl]_A - 6.016,\ r = 0.80 \qquad \text{[Eq. 3]}$$

standard errors of the estimate: 0.0011 for the $([Gl]_A)^2$ term, 0.191 for the $[Gl]_A$ term, 7.061 for the intercept.

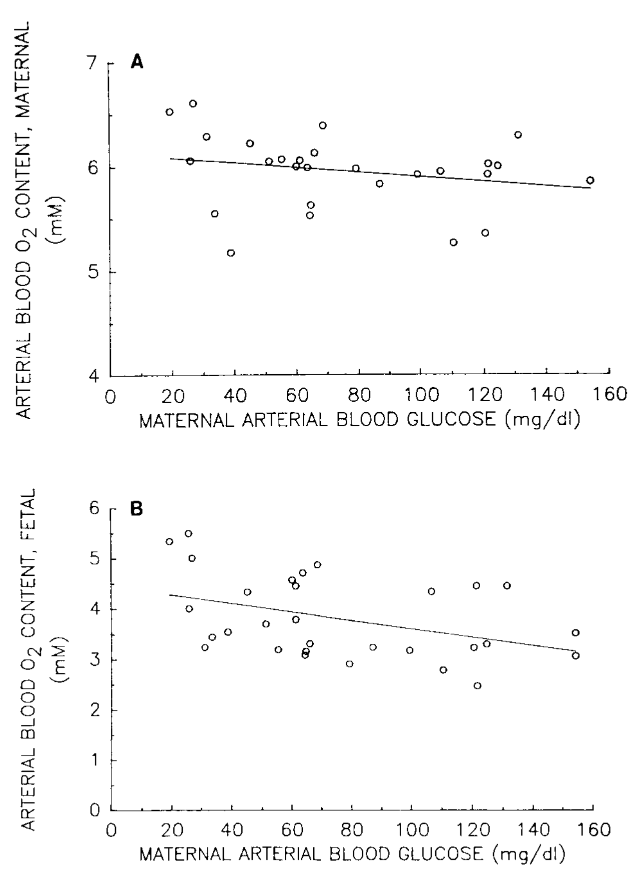

Figure 4. A, Maternal arterial blood oxygen content (O_2A) did not change significantly with $[Gl]_A$: $O_2A = 0.00229\ [Gl]_A + 6.13$, $r = 0.27$, $P > 0.2$. B, Fetal arterial blood oxygen content (O_2a) decreased with $[Gl]_A$: $O_2a = -0.00827\ [Gl]_A + 4.44$, $r = 0.411$, $P < 0.05$.

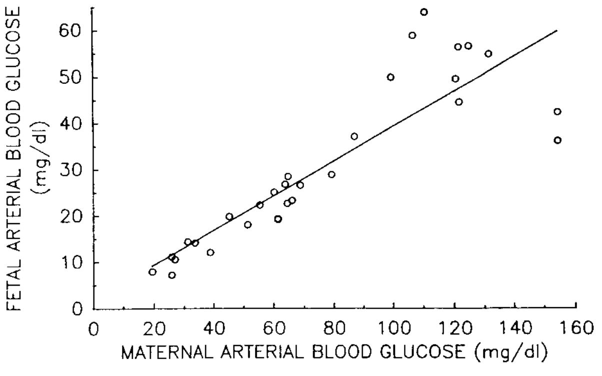

Figure 5. Fetal arterial blood glucose concentration ($[Gl]_a$) increased with maternal arterial blood glucose concentration ($[Gl]_A$): $[Gl]_a = 0.374\ [Gl]_A + 1.82$, $r = 0.873$, $P < 0.001$.

Over the $[Gl]_A$ range studied, UPGC and UPGT were approximately parallel (UPGC = 1.19 UPGT + 3.79, $r = 0.764$, $p < 0.001$) (Fig. 7), and both tended to reach plateau values as $[Gl]_A$ approached 145 mg/dl. The plateau value for UPGT was 32 mg/min and occurred at $[Gl]_A = 165$ mg/dl. The plateau value for UPGC was 41 mg/min and occurred at $[Gl]_A = 145$ mg/dl.

Discussion

The purpose of performing the present study was to determine the relationships between maternal arterial glucose concentration and the net rates of glucose uptake (consumption) and transfer to the fetus by the uteroplacenta. The uteroplacenta represents those tissues interposed anatomically between the uterine and umbilical circulations that serve the primary role of regulating the exchange of nutrients and metabolic products between the maternal and the fetal circulations. To make these measurements a broad range of maternal arterial blood glucose concentrations (19.4 to

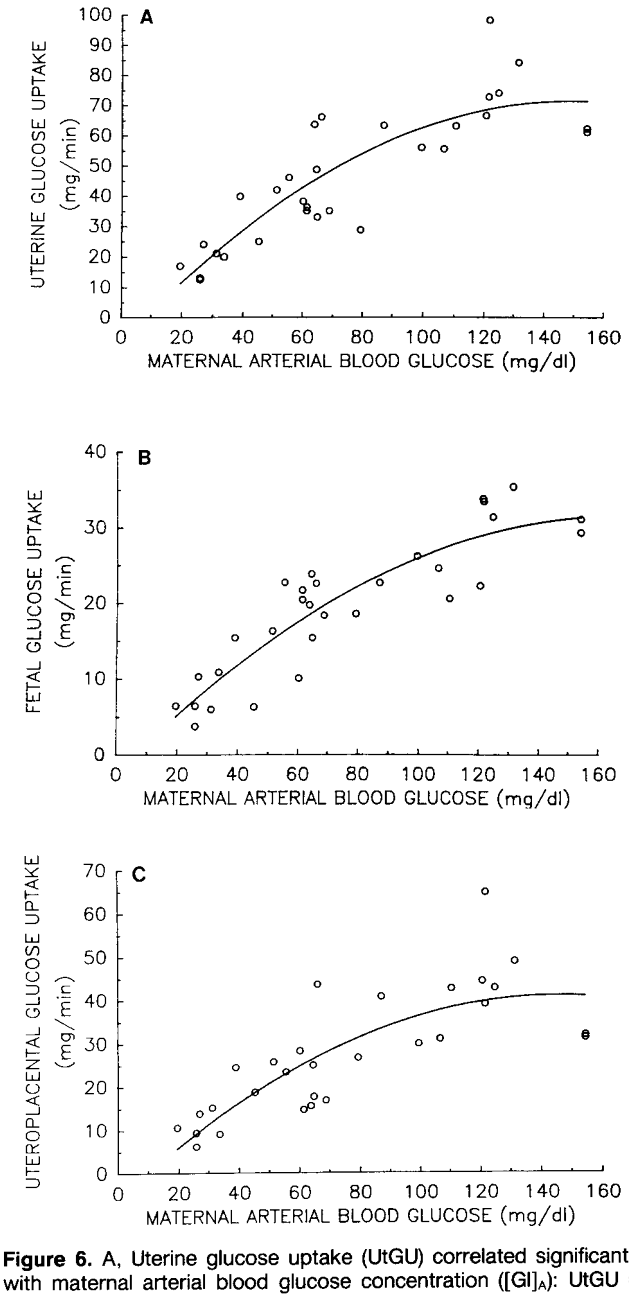

Figure 6. A, Uterine glucose uptake (UtGU) correlated significantly with maternal arterial blood glucose concentration ($[Gl]_A$): $UtGU = -0.003546\ ([Gl]_A)^2 + 2.062\ [Gl]_A - 8.021$, $r = 0.86$, $P < 0.001$. B, Fetal glucose uptake or uteroplacental glucose transfer to the fetus (UPGT) correlated significantly with maternal arterial blood glucose concentration ($[Gl]_A$): $UPGT = -0.001208\ ([Gl]_A)^2 + 0.405\ [Gl]_A - 2.416$, $r = 0.90$, $P < 0.001$. C, Uteroplacental glucose uptake (consumption or UPGC) correlated significantly with maternal arterial blood glucose concentration $[Gl]_A$: $UPGC = -0.002221\ ([Gl]_A)^2 + 0.646\ [Gl]_A - 6.016$, $r = 0.80$, $P < 0.001$.

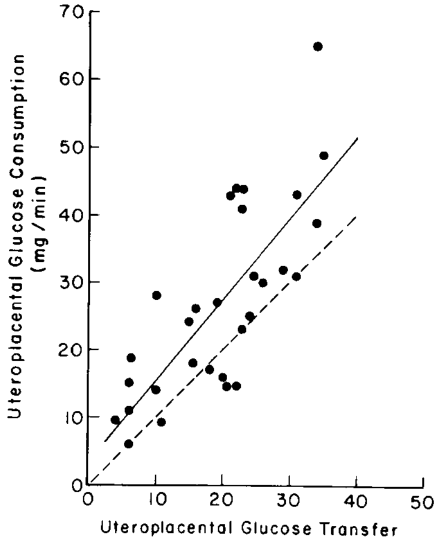

Figure 7. Uteroplacental glucose consumption and uteroplacental glucose transfer are shown to be approximately parallel over the range of maternal glucose concentration studied (solid line, $y = 1.19x + 3.79$, $r = 0.764$, $P < 0.001$). The dotted line represents identity.

154.7 mg/dl) was achieved and regulated by maternal fasting and glucose infusion using a glucose clamp technique. This range of glucose concentrations was selected based on previous measurements of $[Gl]_A$ in fed and fasting pregnant sheep (2, 12) and on the maternal glucose concentration (about 144 mg/dl) at the approximate asymptote value for placental glucose transfer, estimated from the data reported by Crandell *et al.* (13) and Simmons *et al.* (7) in pregnant sheep infused with glucose. The results demonstrate direct and significant relationships between $[Gl]_A$ and net uteroplacental glucose uptake (consumption) and transfer to the fetus, as well as for fetal arterial blood glucose concentration. Fetal blood lactate concentration also correlated directly with $[Gl]_A$, along with a negative correlation between $[Gl]_A$ and fetal blood oxygen content.

UPGC. The important observation of the present study is that, similar to UPGT, glucose consumption by the uteroplacenta was directly related to $[Gl]_A$. In fact, UPGC parallels UPGT over the range of $[Gl]_A$ studied, averaging about 145% of UPGT. These results confirm our earlier hypothesis, based on studying UPGC and UPGT at only two levels of $[Gl]_A$, that UPGC and UPGT co-vary proportionately over the physiologic range of $[Gl]_A$ (2). The meaning of this relationship is obscure in that pathways and regulatory mechanisms of glucose metabolism in the fetal and the uteroplacental tissues are not identical. For example, fructose production by the conceptus appears to be confined to the uteroplacenta (5). Fructose production by the uteroplacenta in sheep is small, averaging about 0.5–1 mg/min/kg fetal wt of 10–20% of simultaneous fetal glucose utilization (5). Fructose production does, however, vary directly with $[Gl]_A$ and $[Gl]_a$. Additionally, although there is a slight tendency noted in this study and in the data reported earlier from our laboratory (6) for lactate production by the uteroplacenta to vary directly with $[Gl]_A$ and UPGC, this tendency is small and not significant. Similar observations have been made by Crandell *et al.* (13). Thus, the increased concentration of lactate found at higher levels of $[Gl]_A$ and $[Gl]_a$ in the present study more likely reflect an increased rate of fetal lactate production. This increased fetal lactate production rate appears to be directly related to fetal glucose utilization and not to fetal hypoxemia or ischemia given the lack of significant change of fetal arterial oxygen content (maximum 15.7% decrease), fetal oxygen consumption, or umbilical blood flow. The fall in fetal arterial oxygen content was small and was not related to a change in fetal oxygen consumption. The most likely explanation for this change is the reduction in fetal oxygen capacity from the replacement of fetal blood samples with maternal blood, which has a lower oxygen affinity and thus a lower oxygen capacity and content at the relatively low PO_2 levels in fetal blood.

To the best of our knowledge, these studies of UPGC vs $[Gl]_A$ have not been performed before in sheep (*in vivo* or *in vitro*) or in other species *in vivo.* Gu and Jones (14) reported an increase of UPGC with $[Gl]_A$ in sheep, but their model was complicated by perturbations that included maternal adrenalin infusion, reduced uterine blood flow, reduced uterine oxygen consumption, and reduced uteroplacental oxygen consumption. In the human placenta studied by *in vitro* perfusion, Hauguel *et al.* (15) demonstrated that UPGC increased disproportionately greater than UPGT at increasing $[Gl]_A$, finally achieving a V_{max} (maximum, plateau value of UPGC) at a Ks ($[Gl]_A$ at V_{max}) of about 20 mM (360 mg/dl) with a K_m ($[Gl]_A$ at $V_{max}/2$) of about 20 mM (100 mg/dl). It remains to be determined to what extent such *in vitro* conditions apply to the *in vivo* state and how closely human placental and ovine uteroplacental tissues function metabolically.

UPGT. Although described best by a curvilinear relationship, the placental transfer of glucose to the fetus (Eq. 2, Results) can be approximated also by a linear slope from about 20 to 140 mg/dl of maternal arterial glucose concentration (UPGT = 0.194 $[Gl]_A$ + 4.475, $r = 0.85$). The slope of this relationship, 0.194 mg/min per mg/dl, is similar to the linear slope (0.24) predicted by the data reported by Simmons *et al.* (7) but less than the linear slope (0.33) estimated from the data reported by Crandell *et al.* (13).

Similarly, the predicted maximum plateau value for UPGT was ~32 mg/min in the present study at a $[Gl]_A$ of ~165 mg/dl, which can be compared with estimated values of V_{max} of 42 mg/min at a $[Gl]_A$ of 155 mg/dl from the data by Simmons *et al.* and 27.7 mg/dl at 144 mg/dl from the data by Crandell *et al.* (13). The reasons for the differences among these values for slope and plateau values of UPGT and $[\mathrm{Gl}]_A$ are not readily apparent, although there is considerably less variation in the data in the present study, reasonably the result of the glucose clamp control, suggesting a more accurate representation of the UPGT versus $[\mathrm{Gl}]_A$ relationship in the present study. Nevertheless, there is sufficient agreement among these three studies to state that in sheep, UPGT changes directly with a change in $[\mathrm{Gl}]_A$ over the physiologic range of $[\mathrm{Gl}]_A$, but above the normal values for $[\mathrm{Gl}]_A$ (>70 mg/dl), UPGT changes disproportionately less than $[\mathrm{Gl}]_A$, reaching a plateau value at about 160 mg/dl $[\mathrm{Gl}]_A$.

These observations are consistent with a carrier-mediated system for UPGT, with saturation of the carrier mechanism(s) at high concentrations of maternal and fetal glucose concentrations. This interpretation has been used by other investigators (13) to propose a carrier model and kinetic constants (e.g., $V_{\max}$, K_m, K_s) for ovine placental transport. However, in other studies in which glucose was infused directly into the fetus, fetal glucose utilization reached a maximum rate of 9-10 mg/min/kg (16), comparable to the mean maximum value of 9.24 mg/min/kg in the present study. Thus, the slope and plateau values of UPGT predicted for the sheep placenta in this study reflect not only uteroplacental glucose transfer kinetics but represent in addition (and perhaps more importantly) the kinetics of fetal glucose uptake and utilization. For this reason, it is not appropriate to use this model and experimental design, as was done by Crandell *et al.* (13), to describe the kinetics of uteroplacental glucose transfer to the fetus. *In vitro* placental perfusion models without the potentially limiting glucose metabolic capacity of the fetus, or *in vivo* models in which $[\mathrm{Gl}]_A$ and $[\mathrm{Gl}]_a$ are varied independently (7), are more appropriate to define the limiting characteristics (e.g., $V_{\max}$, K_m, K_s) of placental glucose transfer.

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