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Uterine Artery Ligation in the Maternal Rat Alters Fetal Tissue Glucose Utilization

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ABSTRACT. We studied the effects of maternal uterine artery ligation on fetal rat tissue glucose utilization (GU). Unilateral uterine artery ligations were performed on the 19th d of gestation (term 21.5 d) and 2-[^{3}H]deoxy-D-glucose was used to measure GU of placenta, liver, brain, muscle, kidney, and heart from fetuses in the ligated (IUGR) and nonligated (control) uterine horns 24 and 48 h after the procedure. At both periods, IUGR fetuses weighed significantly less and had lower fetal/maternal plasma glucose ratios than controls. Twenty-four h after ligation, placenta, liver, brain, and muscle from IUGR fetuses had lower relative GU rates than corresponding tissues from control fetuses ($p < 0.01$–0.05). However, at 48 h, IUGR liver, muscle, kidney, and heart had higher relative GU rates than control tissues ($p < 0.01$–0.05). The lower GU of IUGR fetal tissues observed at 24 h postligation was likely related to the acute decrease in fetal glucose availability. Other factors, such as hypoxemia and acidosis, that affect cellular metabolism may also have led to lower GU rates. The increase in GU by IUGR tissues at 48 h occurred despite a persistence of low fetal glucose concentrations and can be explained by either: *1*) an attempt by IUGR fetal tissues to compensate for the persistently low plasma glucose; *2*) an increased demand for metabolic fuel for repair processes; or *3*) a less efficient use of glucose due to alterations in cellular respiration. We speculate that this increase in fetal tissue GU may be partially responsible for the supranormal glucose requirements seen in small-for-gestational-age newborns. (*Pediatr Res* 28: 464–468, 1990)

Abbreviations

GU, glucose utilization
IUGR, intrauterine growth retardation
LC, lumped constant
P_k, placental discrimination constant
2DG, 2-deoxyglucose
2DG6P, 2-deoxyglucose-6-phosphate

Maternal hypertension, chronic renovascular diseases, and several other conditions are associated with reduced uterine blood flow during pregnancy. These conditions are associated with a high incidence of IUGR and increased fetal and neonatal mortality (1, 2). In addition, growth-retarded neonates are at significant risk for neonatal hypoglycemia (3). The mechanisms by which these conditions retard fetal growth and the processes that are responsible for the neonatal hypoglycemia are not completely understood.

Maternal uterine artery ligation has frequently been used to study the consequences of reduced uterine blood flow on the fetus. This procedure severely retards fetal growth in the rat (4–10). Previous studies using this model have suggested that limited fetal nutrient availability and altered placental gaseous exchange play important roles in the impairment of fetal growth (5, 6). Restricted glucose delivery to the developing fetus leads to low levels of glucose, the primary fetal metabolic substrate, and insulin, an important fetal growth hormone (6). Uterine artery ligation has been shown to produce fetal hypoxia, hypercapnia, and acidosis (6), which likely affect both cellular metabolism and fetal growth. This model is also associated with reduced glycogen stores and delayed induction of gluconeogenic enzymes (7, 8). These processes also appear to be important factors in the development of hypoglycemia in the small-for-gestational-age newborn (11, 12). However, small-for-gestational-age human infants may have increased metabolic rates (13, 14) and rapid clearance of i.v. administered glucose (15, 16), which could also contribute to the development of hypoglycemia.

The effects of uterine artery ligation on fetal GU remain unknown. Knowledge of these effects may further define the mechanisms responsible for altered fetal glucose homeostasis, IUGR, and neonatal hypoglycemia. Studies of fetal GU, however, would be incomplete if individual tissue responses to uterine artery ligation were not considered. Fetal brain growth is minimally, if at all, affected by this procedure, whereas hepatic growth is markedly impaired (4, 5). Therefore, the effects on GU of individual tissues may differ. Furthermore, these effects may change with time after the procedure. We therefore performed unilateral uterine artery ligations on pregnant rats and measured GU of several major fetal tissues from fetuses in the ligated and nonligated uterine horns at 24 and 48 h after ligation.

MATERIALS AND METHODS

We used a modification of Sokoloff's 2DG method to measure fetal rat tissue GU (17–19). 2DG is transported into the cell and phosphorylated by hexokinase or glucokinase in a manner similar to glucose. Because of the absence of the hydroxyl group at position 2, the phosphorylated product, 2DG6P, is not further metabolized (17). The accumulation of 2DG6P within a tissue can therefore be used to determine GU. The standard equation to measure GU of a particular tissue after an i.v. pulse of 2DG is:

$$GU = \frac{[2DG6P]T}{LC\int_0^T \frac{[2DG]t}{[glucose]}\,dt}$$

where [2DG6P] is the tissue concentration of 2DG6P at time T,

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[2DG] and [glucose] are the plasma concentrations of 2DG and glucose, and LC is the lumped constant (20).

LC is a correction factor that accounts for differences of affinities and maximal velocities of transport and phosphorylation between 2DG and glucose. Each tissue has a specific LC; however, due to technical limitations, the LC of individual fetal rat tissues cannot be determined. The above equation without this correction factor provides a measure of relative GU. In our study, we compared relative GU rates of similar tissues from experimental and control fetuses on the assumption that the experimental procedure had not affected the LC.

Measurements of fetal tissue GU require knowledge of the fetal plasma concentrations of 2DG and glucose. However, one cannot sample fetal blood in the unanesthetized rat and, as anesthesia may alter glucose metabolism, measurements of GU must be made in the awake animal. Using the method of Leturque *et al.* (18, 19), we established the relationship between fetal and maternal plasma concentrations of 2DG and glucose after a pulse of 2DG for each of the study and control groups of fetuses in anesthetized rats. This relationship is best expressed as a ratio, which has been termed P_k:

$$P_k = \frac{\int_0^T \frac{[2DG]\ t}{[glucose]}\ dt \text{ (fetal plasma)}}{\int_0^T \frac{[2DG]\ t}{[glucose]}\ dt \text{ (maternal plasma)}}$$

Once P_k is known, relative GU rates of fetal tissues can be measured in the awake animal using maternal arterial plasma concentrations of 2DG and glucose and the fetal tissue concentrations of 2DG6P:

$$\text{Relative GU} = \frac{[2DG6P]\ T \text{ (fetal tissue)}}{P_k \int_0^T \frac{[2DG]\ t}{[glucose]}\ dt \text{ (maternal plasma)}}$$

Surgical procedure. Nine-wk-old pregnant Sprague-Dawley rats were obtained from Harlan Laboratories (Madison, WI), housed separately, and allowed free access to water and food. On d 19 of gestation (term 21.5 d), we anesthetized each maternal rat with intraperitoneal injections of 6 mg/kg xylazine and 30 mg/kg ketamine and made a vertical abdominal incision under sterile conditions.

For GU measurements, the left cervical uterine artery was ligated with a single silk suture. The right uterine horn was similarly manipulated but the artery was not ligated. The left jugular vein and carotid artery were then catheterized with sterile polyvinyl tubing. Rats were excluded from the GU studies if they had fewer than four or greater than seven fetuses per uterine horn or a discrepancy of more than two fetuses between uterine horns.

For P_k determinations, bilateral uterine artery ligations or sham surgeries were performed because eight or more fetal blood samples were required. Catheterizations were done as in the GU studies. All animals were allowed to recover for 24 h before further testing.

This protocol was approved by the Animal Care Committees of Northwestern University and Children's Memorial Hospital.

GU. Relative GU rates of fetal tissues were measured at 24 and 48 h after ligation of the uterine artery. After a 3- to 5-h fast, each rat was placed in a snug but not overly tight restraint. Once the rat was tranquil, 370 kBq (sp act 262.7 kBq/nmol) of [^{3}H]2DG (New England Nuclear, Boston, MA) was injected through the jugular catheter. Maternal blood (100 μL) was obtained through the arterial catheter at 1, 3, 5, 10, 15, 20, 25, 30, 35, and 43 min after the injection. At 44 min, the mother was anesthetized with 40 mg/kg i.v. pentobarbital and her abdominal wound was reopened. At 45 min, three fetuses from the mid-portion of each uterine horn were removed, decapitated, frozen in their entirety in liquid nitrogen, and weighed. All six fetuses were removed and frozen within 2 min. Approximately 100-mg portions of the placenta (villous chorion) and liver, and the entire heart, cerebral hemispheres, kidney, and hind limb muscles were removed from each frozen fetus and weighed. Tissues were placed in 0.5 mL 1 N NaOH, heated to 60°C until completely digested, and then neutralized with 0.5 mL 1 N HCl (21). Tissue homogenates were later assayed for [^{3}H]2DG6P activity.

P_k. P_k were also determined 24 and 48 h after bilateral uterine artery ligations or sham surgery. We anesthetized the maternal rat with 40 mg/kg i.v. pentobarbital, performed a tracheostomy, and ventilated the rat in a fractional inspired oxygen of 0.21 at 80 breaths/min with a tidal volume of 1.7 mL. The abdominal wound was then reopened and covered with warm saline-soaked gauze. Care was taken not to manipulate the uterine horns in a way that would interfere with uterine blood flow. Body temperature was maintained with the use of a heating pad. At time 0, we injected 370 kBq of [^{3}H]2DG into the jugular catheter. Maternal blood was collected at the same times as in the GU studies. Immediately after obtaining each maternal sample, a small hysterotomy was made and a single fetus was exposed leaving the uteroplacental-fetal circulation intact (22). The fetal axillary artery was severed and blood was collected in heparinized capillary tubes. Fetal blood was usually obtained at 2, 4, 6, 11, 16, 21, 26, 31, 36, and 44 min after the 2DG injection.

Analyses. Plasma [^{3}H]2DG activity. Maternal blood (from GU measurements and P_k determinations) and fetal blood (from P_k determinations) were centrifuged at 9000 × *g*. Fifty μL of plasma from each sample were added to 5 mL of scintillation cocktail (Cytoscint, ICN, Cleveland, OH) and counted for 10 min. The plasma glucose concentration of each sample was determined in duplicate (Beckman Glucose Analyzer II).

Tissue [^{3}H]2DG6P activity. To separate tissue 2DG from 2DG6P, we used a method based on the principle that although both 2DG and 2DG6P are soluble in 5% $HClO_4$, only 2DG remains soluble in a $Ba(OH)_2/ZnSO_4$ mixture (23). One 400-μL aliquot of tissue homogenate was added to 1.0 mL of 5% $HClO_4$ and a second 400-μL aliquot was added to 0.5 mL $Ba(OH)_2$ (Sigma Chemical Co., St. Louis, MO), followed by the addition of 0.5 mL $ZnSO_4$ (Sigma). After centrifugation, 700 μL of each supernatant was added to 20 mL of scintillation cocktail and counted for 10 min. The difference in radioactivity between the $HClO_4$- and $Ba(OH)_2/ZnSO_4$-treated samples was used as the tissue [^{3}H]2DG6P activity.

Calculations. P_k determinations. The ratio of [^{3}H]2DG activity to glucose concentration for each maternal and fetal plasma sample was plotted *versus* time (Fig. 1). The area under the maternal curve from time 0 to 45 min was obtained by establishing the best-fit curve using the double exponential equation: $y = Ae^{Bx} + Ce^{Dx} + E$; where A, B, C, D, and E are constants chosen by a curve-fitting program. The integral of the equation was then calculated. Because the fetal plasma [^{3}H]2DG activity did not peak immediately after the 2DG injection, the area under the fetal curve from time 0 to the peak [2DG]/[glucose] value was determined separately. The area under the remaining fetal curve from the peak value to 45 min was calculated using the best-fit curve method. The ratio of the area under the fetal curve to the area under the maternal curve is equivalent to the P_k.

GU measurements. The ratio of [^{3}H]2DG activity to glucose concentration for each maternal plasma sample was plotted *versus* time. The area under the curve from time 0 to 45 min was obtained, as before, using the best-fit curve method. The value of the integral was corrected by the previously determined P_k. The relative GU of a specific fetal tissue for a single experiment was calculated by dividing the average 2DG6P activity of that tissue from the three fetuses of either the ligated or nonligated uterine horn by the corrected value of the integral.

Statistical analysis. We used unpaired, one-tailed *t* tests to determine differences between IUGR and control fetal weights. Group differences of P_k values and fetal/maternal glucose ratios were determined by analysis of variance. Paired, two-tailed *t* tests

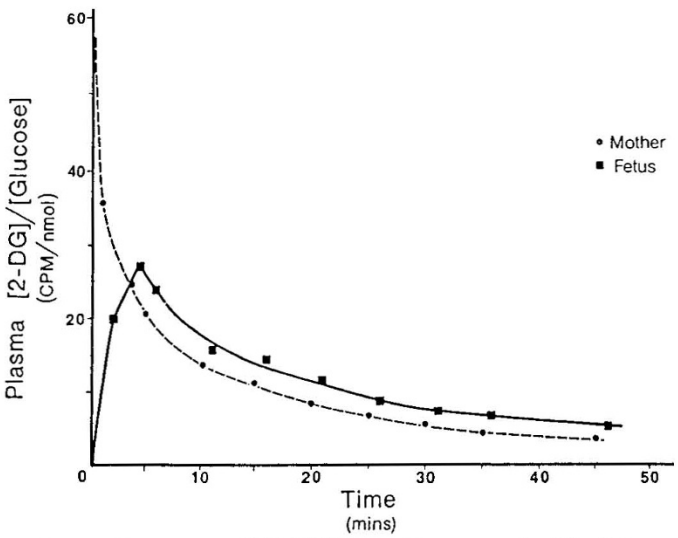

Fig. 1. Time course of [2DG]/[Glucose] in maternal and fetal plasma after a single maternal i.v. injection of [^{3}H]2-deoxyglucose. Best-fit curves were generated using a double exponential equation. The ratio of the areas under the fetal and maternal curves were used as the P_k.

were used to analyze GU differences between IUGR and control fetal tissues. Data are presented as mean ± SEM.

RESULTS

Fetal weight. At 24 h after uterine artery ligation, IUGR and control fetuses weighed 3.02 ± 0.14 and 3.37 ± 0.13 g, respectively ($p < 0.05$). At 48 h, IUGR fetuses weighed 3.61 ± 0.11 g, whereas control fetuses weighed 4.70 ± 0.08 grams ($p < 0.005$).

P_k and fetal maternal glucose. Uterine artery ligation resulted in significantly greater mean P_k values at 24 and 48 h postligation (Table 1). Although maternal IUGR and control plasma glucose concentrations were similar, IUGR fetuses had significantly lower plasma glucose concentrations than controls at both periods, resulting in lower fetal/maternal glucose ratios. Uterine artery ligation was associated with reductions in the fetal/maternal glucose ratio of 19.2% at 24 h and 14.4% at 48 h.

GU studies. At 24 h postligation, placenta, liver, brain, and muscle from IUGR fetuses had lower relative GU rates than the respective tissues from control fetuses. Relative GU of kidney and heart were similar in IUGR and control fetuses (Fig. 2).

At 48 h, IUGR liver, muscle, kidney, and heart had higher relative GU rates than the control fetuses. Relative GU rates of placenta and brain did not differ between IUGR and control fetuses at this time (Fig. 3).

DISCUSSION

We found a biphasic response of fetal rat tissue GU after uterine artery ligation. At 24 h postligation, placenta, liver, cerebral hemispheres, and hind limb muscle from IUGR fetuses had lower relative GU rates than the corresponding tissues from control fetuses. However, at 48 h, GU was higher in IUGR liver, hind limb muscle, kidney, and heart. All IUGR tissues demonstrated an increase in GU, relative to control, from 24 to 48 h postligation, with liver and muscle showing the greatest changes. IUGR tissues demonstrated an average decrease in GU of 8.2% at 24 h and an average increase of 22.2% at 48 h after uterine artery ligation.

Our results concur with two earlier studies. Nitzan and Groffman (9) found an increased uptake of ^{14}C-glucose *in vitro* by IUGR liver slices but not by IUGR brain slices at term after uterine artery ligation in the rat. In a separate *in vivo* study, they found a relatively greater uptake of 2DG by several IUGR rat fetal tissues 2 d after uterine artery ligation (5). However, because of their methodology, they could not quantitate fetal tissue GU. Our results are also supported by reports of increased glucose disappearance rates in hypoglycemic IUGR human newborns (15, 16). This observation has been considered to be the result of "growth-sparing" of metabolically active organs, *e.g.* brain and heart. Our data suggest that absolute increases in IUGR tissue GU may be partially responsible for these elevated glucose requirements.

We used a modification of the 2DG method described by Leturque *et al.* (18, 19) to measure relative GU rates of fetal rat tissue. In addition to the criteria described by Sokoloff *et al.* (17) for the original 2DG method, two further assumptions must be made: *1*) glucose-6-phosphatase activity of fetal tissues is negligible or, if present, is similar between IUGR and control fetuses; and *2*) the LC of fetal tissues is not affected by uterine artery ligation.

Glucose-6-phosphatase is only found in large concentrations in postnatal rat liver, kidney, and intestine (24). Although glucose-6-phosphatase is present in fetal rat liver and kidney, its activity remains low until birth (24–26). Small concentrations of this enzyme, however, may result in falsely low GU rates as calculated by the 2DG method (27). Our observation of higher GU of IUGR liver and kidney at 48 h postligation could have resulted from a delay in glucose-6-phosphatase induction not seen in controls. However, fetal hypoglycemia and hypoinsulinemia, as produced by maternal fasting or insulin infusion, increases glucose-6-phosphatase activity in fetal liver (28). Inasmuch as maternal uterine artery ligation also produces fetal hypoglycemia and hypoinsulinemia, IUGR fetal tissues would be expected to have higher enzyme activity than controls, thus resulting in lower rather than higher GU rates. Although the second assumption cannot be verified, it is doubtful that uterine artery ligation should have produced a change in the Km or V_{max} of a tissue's transporter or hexokinase for 2DG without equally affecting that for glucose.

The P_k accounts for differences in 2DG and glucose concentrations between maternal and fetal plasma after the administration of 2DG to the mother. The value of this ratio is influenced by at least three processes: *1*) a lag period between the injection of 2DG into the maternal vein and its appearance in the fetal circulation (Fig. 1); *2*) a greater affinity of the glucose transporter for 2DG over glucose; and *3*) a lesser affinity of placental hexokinase for 2DG. The first process will tend to decrease the value of P_k, whereas the second and third processes will tend to

Table 1. *P_k and fetal/maternal glucose ratios (mean ± SEM)*

	P_k	Maternal glucose (mmol/L)	Fetal glucose (mmol/L)	Fetal/Maternal glucose
24 h postligation				
IUGR ($n = 8$)	1.21 ± 0.03*	5.6 ± 0.2	2.7 ± 0.2*	0.49 ± 0.02†
Control ($n = 8$)	1.10 ± 0.02*	5.3 ± 0.2	3.2 ± 0.1*	0.61 ± 0.01†
48 h postligation				
IUGR ($n = 7$)	0.95 ± 0.03*	5.2 ± 0.5	3.6 ± 0.3*	0.69 ± 0.01†
Control ($n = 7$)	0.93 ± 0.01*	5.2 ± 0.4	4.2 ± 0.3*	0.80 ± 0.03†

* $p < 0.05$ IUGR *vs* control.
† $p < 0.005$ IUGR *vs* control.

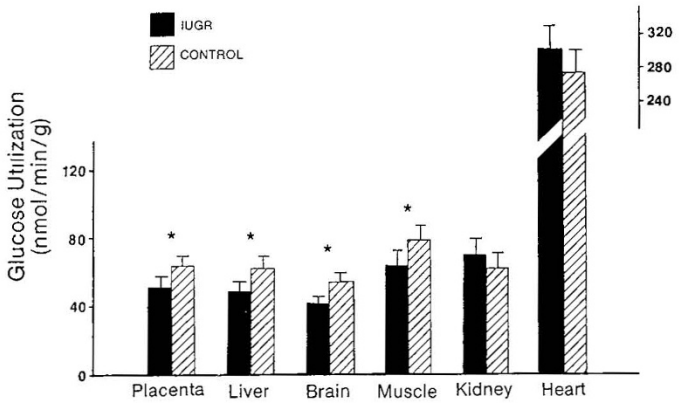

Fig. 2. Relative GU rates of fetal rat tissues 24 h after unilateral uterine artery ligation. * indicates significant differences between IUGR and control fetal tissue ($p < 0.05$ to $p < 0.01$). $n = 9$ experiments.

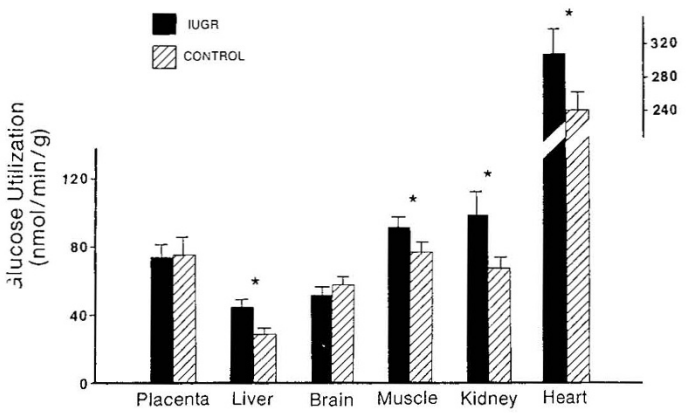

Fig. 3. Relative GU rates of fetal rat tissues 48 h after unilateral uterine artery ligation. * indicates $p < 0.05$ to $p < 0.01$. $n = 7$ experiments.

increase P_k. We found significantly higher P_k values after uterine artery ligation. This finding may be explained by the production by the IUGR placenta of glucose transporters with relatively greater affinity for 2DG or hexokinases with relatively lower affinity for 2DG. Alternatively, with reduced uterine blood flow, a higher percentage of glucose and 2DG may have been extracted from the maternal circulation. This may have induced a change in the placental LC, thus explaining the higher P_k values in IUGR fetuses.

After 2DG administration to pregnant Wistar rats on d 19 of gestation, Leturque *et al.* (19) measured the ratio of the integrals of maternal to fetal blood 2DG/glucose, which is the inverse of our P_k. They obtained a value of 0.87 ± 0.02, the inverse of which (1.15) compares favorably with our 24 h control value. They also measured GU of placenta, liver, brain, muscle, and heart from d 19 fetuses during maternal hyperglycemic and euglycemic hyperinsulinemic clamp experiments (19, 20). They found GU rates of their control fetal tissues somewhat higher than those we observed for our respective control tissues. This difference may be due to the use of a different rat stain or use of a different P_k value.

Several mechanisms may explain the differences in GU rates between IUGR and control tissues. The lower GU of IUGR tissues 24 h postligation is probably due to the acute decrease in fetal plasma glucose concentrations. Alterations in other factors that affect cellular metabolism such as hypoxia-induced reduction of cellular metabolism could also have affected GU.

The higher relative GU rates of IUGR tissues at 48 h postligation were not anticipated. They occurred despite a persistence of low fetal plasma glucose concentrations. In addition, we have previously documented low insulin levels in IUGR fetuses 48 h after uterine artery ligation (6). The mechanisms responsible for the paradoxical increase in uptake and phosphorylation of 2DG (and thus glucose) are not clear. This finding may reflect an adaptation or compensation by fetal tissues in response to persistently low glucose concentrations. By increasing the number of glucose transporters or the amount of hexokinase, fetal tissues would be more able to extract glucose from plasma. Other studies support this mechanism. Rat skeletal muscle cells up-regulate their 2DG uptake and have higher levels of glucose transporter mRNA when exposed to low (2 mM) glucose (29). Similarly, brains from chronically glucose-starved rats have elevated glucose transporter mRNA levels (30).

The higher GU may also be the result of an increased demand for metabolic fuel by IUGR tissues. Cellular death and structural damage are likely consequences of uterine artery ligation. Repair processes would require additional energy and thus could account for the elevated rates of GU. Alternatively, the increased demand for glucose may be explained by a decreased oxidation of carbons arising from glucose, which, in turn, is compensated for by increased glycolysis. Maternal uterine artery ligation significantly reduces the ATP/ADP ratio and profoundly alters cytosolic and mitochondrial redox states in fetal liver (31). These findings indicate a disruption of cellular respiration resulting in less ATP generated per unit glucose used. Because hexokinase, the rate-limiting enzyme of glycolysis, is inhibited by ATP and stimulated by ADP, this process could lead to increased GU by IUGR fetal tissues.

Additional factors may contribute to the relatively higher GU by IUGR fetal tissues. Collateral uterine circulation may be developing by 48 h after ligation. Although serial measurements of uterine/placental blood flow after uterine artery ligation are lacking, some investigators have found a persistence of reduced placental blood flow when expressed as mL/min at 3 and 4 d postligation (32, 33). Higher fetal glucose concentrations and fetal/maternal glucose ratios were observed at 48 h postligation for both IUGR and control fetuses. Although the IUGR fetal/maternal glucose ratio remained significantly lower than control, the increase in IUGR fetal glucose may reflect an improved availability of glucose that contributed to the higher GU rates of IUGR tissues. Although fetal insulin levels were not measured in our study, we have previously demonstrated low insulin concentrations in IUGR fetuses 48 h after ligation. This observation argues against the speculation of higher glucose availability and rules out the possibility of high insulin as a cause of the increased GU of IUGR tissues.

It should be noted that the GU of control liver decreases from d 20 to 21 (Figs. 2 and 3). This was not observed in IUGR liver and thus accounts for the relatively higher GU of IUGR liver at 48 h postligation. The cause of the lower GU of control liver at 48 h is not known but may reflect maturational processes such as completion of glycogen deposition.

IUGR neonates have been reported to have significantly increased energy requirements and are at risk of developing hypoglycemia compared with normally grown infants (3). The development of hypoglycemia results in part from limited hepatic glycogen stores and diminished gluconeogenic capability (11, 12). We speculate that a carryover of the increased tissue GU from fetal to neonatal life may also contribute to the development of hypoglycemia and the increased energy requirements.

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