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Research Article

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Effects of Chronic Fetal Hyperglycemia upon Oxygen Consumption in the Ovine Uterus and Conceptus

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Abstract. Hyperglycemia has been shown to induce arterial hypoxemia in the chronically catheterized fetal sheep. To investigate the mechanism behind this glucose-induced hypoxemia, eight pregnant ewes and their fetuses were studied. Fetal glucose infusion (11.9 ± 0.6 mg glucose/kg per min) was associated with a doubling of the fetal plasma glucose concentration with concomitant elevation of the umbilical vein-distal arterial O_2 content difference by 24 h of infusion ($P < 0.01$). Calculated fetal O_2 consumption increased from 8.1 ± 0.4 ml/kg per min in the control period to a maximum value of 10.6 ± 0.3 ml/kg per min by third infusion day ($P < 0.01$), which is an increase of $\sim 30\%$. The degree of stimulation of fetal O_2 consumption was related to the degree of fetal hyperglycemia but not to the degree of fetal hyperinsulinemia. The increase in fetal O_2 consumption was accompanied by a significant increase in fetal O_2 extraction with no change in either fetal O_2 delivery or fetal blood O_2 affinity. In addition, fetal hypercapnea with a mild fetal respiratory acidosis was induced by fetal hyperglycemia. The increase in fetal arterial PCO_2 was linearly related ($P < 0.001$) to the magnitude of increase in fetal O_2 consumption. These studies suggest that chronic fetal hyperglycemia induces a state of accelerated fetal oxidative metabolism and may be important in explaining the etiology behind certain unusual findings in human infants of diabetic mothers.

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Introduction

The classical findings of macrosomia and postnatal hypoglycemia in newborn infants born to women with diabetes mellitus are thought to be due to the excesses in substrate uptake and insulin secretion of the fetus (1, 2). However, certain clinical and pathological findings suggest that other disorders seen in these infants, such as polycythemia, hyperbilirubinemia, and late fetal demise (2, 3), may be related to occult in utero hypoxemia. Using a chronically catheterized fetal lamb preparation, it has recently been demonstrated that long-term fetal glucose infusion induces a relative fetal arterial hypoxemia (4), and that the degree of this hypoxemia is related to the magnitude of the hyperglycemia. It has been unclear whether or not this glucose-induced hypoxemia is secondary to abnormalities in uterine and/or fetal oxidative metabolism or is simply due to altered placental gas transport. The purpose of the current study was to investigate each of these possible etiologies using the fetal lamb model with chronic defined fetal glucose infusions.

Methods

Surgical preparation. Eight pregnant ewes were studied between 120 and 140-d gestation (term gestation in the sheep is ~ 150 d). Five had singleton pregnancies. Preoperatively, all ewes were anesthetized with intravenous sodium pentobarbital and intrathecal pontocaine. At hysterotomy, polyvinyl chloride catheters were implanted into the fetal distal aorta (postductal) and inferior vena cava using a pedal approach. Of the three twin gestations, only one fetal twin from each was catheterized. Umbilical venous catheters were inserted directly into the common umbilical vein (5) or into a cotyledonary branch and advanced proximally until the catheter tip was in the common umbilical vein. Maternal catheters were placed in the distal aorta via a femoral insertion and into the common uterine vein of the pregnant uterine horn (5). An amniotic space catheter was inserted for pressure monitoring and instillation of antibiotics. All catheters were then tunneled subcutaneously to a pouch on the ewe's flank. Catheter tip placement was confirmed at autopsy in the majority of preparations and was adequate in all. A 4-5-d postoperative recovery period was allowed prior to experimentation. Postoperative management was performed as previously described (6). All animals were housed in individual carts for the duration of the experimental protocol and allowed food and water ad libitum.

Experimental protocol. During a control period of 2 d, fetal and maternal arterial blood samples were obtained for plasma concentrations

of glucose and insulin as well as arterial blood gases (pH, PCO₂ and PO₂), hematocrit, and serum solids. Twice daily, samples were drawn simultaneously from the uterine vein and maternal aorta, and the umbilical vein and fetal distal aorta to assess venoarterial blood concentration differences of oxygen (O₂) across the uterine and umbilical circulations. Uterine and umbilical blood flows were also measured twice daily using the antipyrine steady state diffusion technique (7). Uterine and fetal O₂ consumptions (Q_{O₂})¹ were calculated from the Fick Principle as the product of the respective blood flow and arteriovenous O₂ content difference measurements. Uteroplacental O₂ consumption was derived as the difference between uterine and fetal Q_{O₂}'s. Fetal O₂ delivery was calculated as the product of umbilical blood flow and umbilical venous O₂ content. Fetal O₂ extraction was calculated as the ratio between fetal O₂ consumption and fetal O₂ delivery.

At the end of the 2-d control period, fetal glucose infusion was begun at a rate of 12.5 mg glucose/kg estimated fetal weight per min and continued for 72 h. A solution of 50% glucose in sterile water was infused into the fetal vena caval catheter using precalibrated syringe pumps (Orion Research Products, Cambridge, MA; Harvard Apparatus Co., South Natick, MA). These infusions resulted in infusate delivery rates between 3 and 6 ml/h. At daily intervals beginning 24 h after the commencement of fetal glucose infusion, venoarterial sampling across the uterine and umbilical circulations was performed twice for estimation of blood flow, blood O₂ content, and calculation of O₂ consumption. Since the determination of the rate of fetal weight gain with advancing gestational age was impossible during the experiments, the estimates of fetal oxygen consumption were calculated arbitrarily using the estimated preinfusion weight for control and experimental values alike. Fetal weight increases by ~2-4%/d in late gestation (8) and some, but not proportionate, increases in fetal oxygen consumption (expressed as ml/min) also occur after 120-130-d gestation (9, 10). However, when expressed on a per weight basis, fetal oxygen consumption falls during this period. Thus, the assignment of control fetal weight to the above calculations should not obscure significant changes in fetal oxygen consumption. Four fetuses of similar gestational age were used as controls to adjust for the possible increases in oxygen consumption due to advancing gestational age. Samples were obtained 5 d apart from appropriate fetal vascular catheters and analyzed for blood flow, O₂ content, and calculations of fetal O₂ consumption. In addition, samples of daily maternal and fetal arterial blood were obtained for measurement of plasma glucose and insulin concentrations, blood gases, hematocrit, and serum solids. In selected experiments, fetal arterial blood at 50% saturation (P₅₀) and erythrocyte 2,3-diphosphoglycerate (2,3-DPG) concentration were assessed serially to note any possible alterations in fetal hemoglobin-O₂ affinity.

During control and experimental periods, fetal heart rate and arteriovenous blood pressure differences across the uterine and umbilical circulations were measured using Statham P23-Ia pressure transducers (Statham Laboratories, Hato Rey, PR) and a Hewlett Packard HP7796A Physiologic Recorder (Hewlett-Packard Co., Waltham, MA). Pressure transducers were calibrated against a standard mercury manometer. Fetal arterial and umbilical venous pressures were measured using the intraamniotic fluid pressure as a zero reference. Uterine and umbilical vascular resistances were calculated as the ratio between the appropriate arteriovenous pressure difference and the respective blood flow.

1. *Abbreviations used in this paper:* 2,3-DPG, 2,3-diphosphoglycerate; IDM, infants of diabetic mothers; P₅₀, arterial blood at 50% saturation; Q_{O₂}, fetal O₂ consumption.

Biochemical methods. Plasma glucose concentrations were measured using a glucose oxidase technique (Beckman Instruments, Inc., Palo Alto, CA). Whole blood O₂ content was measured using a Lex-O₂-Con (Lexington Instruments, Waltham, MA) calibrated daily against distilled water saturated with O₂ at 0°C. Blood for O₂ content determinations were withdrawn into capillary tubes pretreated with NaF. Plasma antipyrine concentrations were determined using the Technicon Autoanalyzer (Technicon Instruments Corp., Tarrytown, NY). Arterial blood gases were measured using a Corning #178 Blood Gas Analyzer (Corning Medical Products, Medfield, MA). P₅₀ measurements were performed at 37°C and utilized a tonometric method (IL237 tonometer; Instrumentation Laboratory, Inc., Lexington, MA). Fetal erythrocyte 2,3-DPG concentrations were measured using the enzymatic method of Keitt (11). Plasma insulin concentrations were determined using a modified insulin radioimmunoassay (6) with ovine insulin standards (kindly supplied by Dr. M. A. Root, Eli Lilly Laboratories, Indianapolis, IN).

Statistical methods. All results are expressed as mean±1 SEM. Statistical significance was assessed using the paired Student's *t* test and two-way analyses of variance. Linear regression analyses were performed using the least squares method.

Results

Nine separate glucose infusions were performed in the fetal lambs. Glucose infusion rates were 11.9±0.6 mg glucose/kg per min when corrected for known fetal delivery weights. As shown in Fig. 1, fetal glucose infusion resulted in a sustained increase in fetal plasma arterial glucose concentration from 26.0±1.9 to 58.8±3.7 mg/dl during the 72-h infusion period (*P* < 0.001). Umbilical venous O₂ content fell slightly from 10.7±0.6 to 9.2±0.9 mg/dl, but the change was not statistically significant. In contrast, fetal distal aortic O₂ content fell from the basal value of 7.3±0.5 to 5.7±0.4 ml/dl by 24 h of infusion (*P* < 0.01) and reached a nadir of 4.9±0.7 ml/dl (2.2±0.4 ml/dl below base line) by the third day of glucose infusion (*P* < 0.01). Consequently, fetal hyperglycemia induced a rise in the umbilical venoarterial O₂ content difference by 24 h of infusion (from 3.5±0.2 to 4.3±0.2 ml/dl, *P* < 0.01). The elevation in umbilical (venoarterial) O₂ content was maintained throughout the experimental period (Fig. 1).

Glucose infusion produced no alteration in umbilical blood flow from the basal value of 232±7 ml/kg per min (828±25 ml/min). Control fetal Q_{O₂} as calculated from the Fick equation was 8.1±0.4 ml/kg per min. During fetal hyperglycemia, fetal Q_{O₂} rose to 9.4±0.3 ml/kg per min by day 1 of infusion and to a maximum value of 10.6±0.3 ml/kg per min by day 3 (ΔQ_{O₂} = +2.6±1.6 ml/kg per min, *P* < 0.01). When pooled individual values for the fetal Q_{O₂} were compared with their paired plasma arterial glucose concentrations (Fig. 2), a significant (*P* < 0.001) relationship was apparent between the degree of fetal glycemia and stimulation of fetal oxygen consumption.

The calculations of fetal O₂ delivery and extraction during fetal hyperglycemia in the experimental animals are presented in Table I. Although a fall in fetal O₂ delivery was noted at 24 h of glucose infusion, this change amounted to a < 7% fall from base line and was statistically insignificant. In contrast, fetal O₂

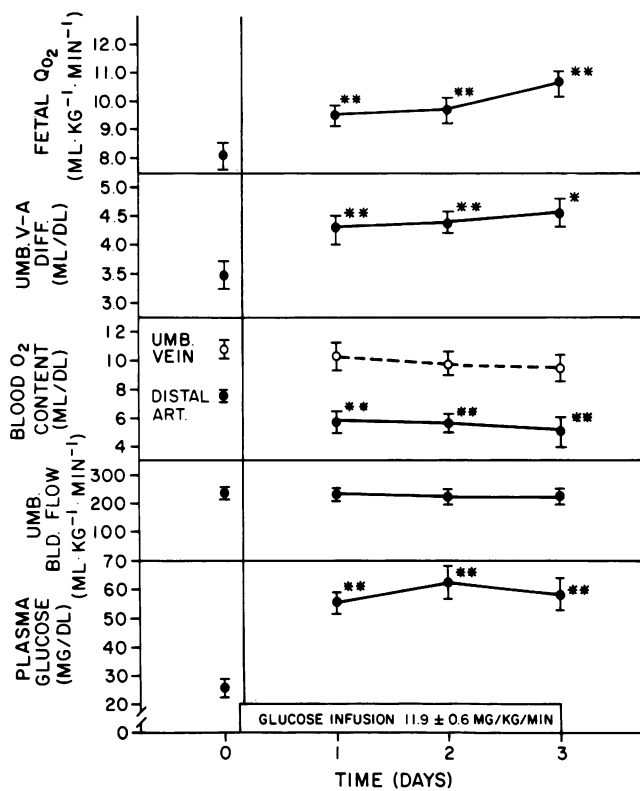


Figure 1. Fetal plasma glucose concentrations, umbilical blood flow (umb. bld. flow), and fetal O₂ contents and consumptions (Q_{O₂}) before and during nine glucose infusions in eight fetal lambs. *, *P* < 0.05; **, *P* < 0.01.

extraction increased successively above the basal value of 33.8±2.5% to a maximum of 51.4±4.5% (*P* < 0.01) by day 3 of infusion.

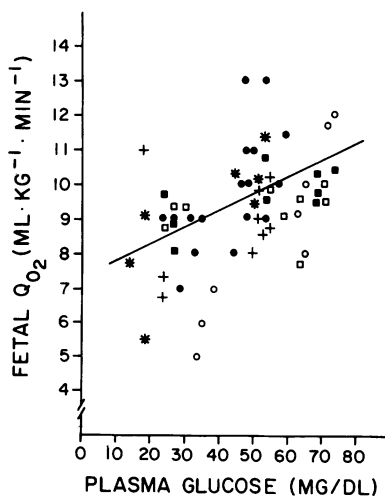


Figure 2. Relationship between fetal plasma glucose concentrations and Q_{O₂} during control and experimental periods. Each symbol represents a different animal preparation. (*n* = 59, *r* = 0.46, *y* = 0.05 *x* + 7.17, *P* < 0.001).

Table 1. Comparison between Fetal Oxygen Delivery and Oxygen Extraction before and during Fetal Glucose Infusion

	Control	Day 1	Day 2	Day 3
Fetal O ₂ delivery (ml/kg per min)	24.8±1.6	22.6±1.7	21.4±1.7	21.7±1.8
Fetal O ₂ extraction (%)	33.8±2.5	42.7±3.0**	46.4±2.6**	51.4±4.5**

** *P* < 0.01, difference from control.

In contrast, fetal oxygen consumption in the four control fetuses increased from 23.8±2.2 to 24.4±2.8 ml/min (8.5±0.8 to 8.7±0.9 ml/kg per min) over a 5-d period similar to that between initiation and completion of each infusion experiment. This elevation amounted to a 3% increase in Q_{O₂} due to advancing gestational age.

In seven of the glucose infusion experiments, simultaneous sampling from the uterine as well as the umbilical circulation was performed through the majority of the experimental period. Although a trend was evident, no changes in uterine venous or arterial O₂ content nor in uterine blood flow were noted from base line. As shown in Fig. 3, although the calculated uterine Q_{O₂} rose from 50.4±4.9 ml/min to a maximum value of 57.8±7.5 ml/min by day 3 of infusion, this change was not statistically significant. Umbilical Q_{O₂} (not corrected for fetal weight) rose

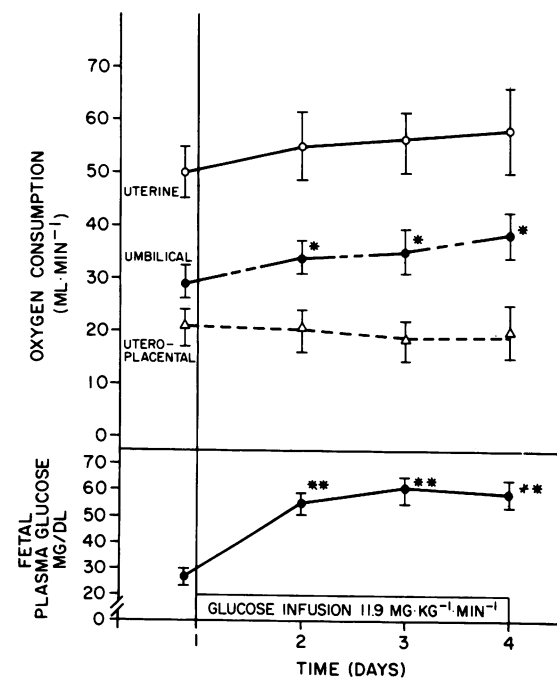


Figure 3. Changes in fetal plasma glucose concentration and O₂ consumption of uterus, fetus (umbilical), and utero placental mass occurring during fetal glucose infusion. (**P* < 0.05).

Table II. Vascular Parameters in Uterine and Umbilical Circulations before and during Fetal Hyperglycemia

	Blood flow (F) (ml/kg/min)		Fetal heart rate beats/min	A-V Pressure (P) difference (torr)		Vascular resistance (R) (torr/ml/kg/min)	
	F _{ut}	F _{umb}		P _{ut}	P _{umb}	R _{ut}	R _{umb}
Control	395±36 (7)*	228±9 (8)	186±7 (8)	69±3 (8)	30±3 (8)	0.19±0.03 (8)	0.14±0.02 (8)
Day 1	394±34 (7)	219±11 (8)	203±11 (8)	70±5 (7)	29±2 (8)	0.19±0.03 (7)	0.13±0.02 (7)
Day 2	396±37 (7)	223±13 (8)	197±10 (8)	67±4 (7)	31±3 (7)	0.18±0.03 (7)	0.14±0.02 (6)
Day 3	416±67 (5)	241±15 (7)	197±12 (7)	71±4 (5)	32±3 (5)	0.20±0.05 (5)	0.13±0.01 (6)

ut, uterine; umb, umbilical. *, (), number of observations.

to a similar degree as the uterine Q_{O₂} (from 29.4±3 to 38.5±4.1 ml/min by day 3 of glucose infusion, *P* < 0.05), and thus, no change in the calculated uteroplacental Q_{O₂} was noted from the basal value of 21.6±2.6 ml/min.

Fetal hyperglycemia induced no alterations in fetal heart rate nor in fetal or maternal blood pressures (Table II). In addition, no changes were seen in uterine or umbilical vascular resistances. No changes in fetal hematocrit nor in total serum solids were detected (Table III). The 50% hemoglobin-O₂ saturation point (P₅₀) of fetal distal arterial blood was determined during five of the infusions (Table III). Hyperglycemia did not change the basal P₅₀ of 15.8±0.6 torr. In four experiments, fetal

Table III. Comparison of Changes in Fetal Arterial Blood Gases and Hemoglobin-oxygen Affinity before and during Fetal Glucose Infusion

	Fetal Arterial Blood Values			
	Day 0	1	2	3
Hematocrit (%)	33.9±0.9 (9)	30.4±3.7 (9)	32.8±1.3 (9)	31.0±1.3 (9)
pH	7.39±0.01	7.36±0.01*	7.40±0.01	7.39±0.01
PCO ₂ (torr)	44.2±2.1	48.0±1.6*	48.6±1.7‡	46.9±1.7
PO ₂ (torr)	17.1±0.9	15.7±1.1	14.2±0.5‡	15.1±1.0*
Base excess (meq/liter)	+1.6±0.9	+1.3±1.4	+4.3±1.0‡	+3.0±1.0
Total serum solids (g/dl)	4.1±0.1	4.2±0.1	4.2±0.1	4.4±0.1
	Control		Day 3	
Arterial P ₅₀ (torr)	15.8±0.6 (5)		15.6±0.8	
2,3-DPG (mol/ml erythrocyte)	1.49±0.20 (4)		1.32±0.24	

Difference from control: *, *P* < 0.05; ‡, *P* < 0.01.

erythrocyte 2,3-DPG concentrations were determined as well and were unaltered by chronic hyperglycemia.

Fetal arterial blood gases assessed daily showed significant changes during hyperglycemia (Table III). As expected, arterial PO₂ fell significantly (*P* < 0.01) by 48 h of glucose infusion. Arterial PCO₂ rose significantly by 24 h of glucose infusion and remained elevated throughout the experimental period, although this elevation was significant on days 1 and 2 only. This hypercapnea was accompanied by a significant fall in pH on day 1 with a subsequent increase in calculated buffer base noted on day 2. The sum total of events indicated an early respiratory acidosis induced by hyperglycemia, with later metabolic compensation and an ongoing arterial hypoxemia. No changes in maternal pH or PO₂ were noted during the experimental period from control. Maternal arterial PCO₂ during the control period was 32.6±1.5 torr and did not change significantly during days 1 and 2 of fetal glucose infusion. A small but statistically significant decrease in PCO₂ to 30.3±1.2 torr (*P* < 0.02) was noted on day 3 of infusion. When the fetal PCO₂ data were related to changes in fetal Q_{O₂}, no relationship was apparent because of interanimal variability in both parameters. However, when fetal Q_{O₂}'s were expressed as percent from control and fetal PCO₂'s expressed as fetomaternal ratios to decrease this variability, a relationship is apparent (Fig. 4). One unusual animal (open circles) responded to hyperglycemia with a large increase in Q_{O₂} but little change in fetal arterial PCO₂. It is unclear whether or not the observed changes in this animal represented experimental error or a true lack of response. Without the addition of this animal to the data, a highly significant relationship (*P* < 0.001) is apparent between fetal Q_{O₂} and fetal PCO₂.

Fetal hyperglycemia induced significant elevations in fetal plasma arterial insulin concentration from a control value of 12.5±1.8 μU/ml to a peak concentration of 28.9±8.3 μU/ml by day 2 of infusion (*P* < 0.01). Overall insulin response, however, was quite variable between animals. One fetus (+) appeared not to respond to glucose infusion with any rise in insulin concentration. Use of weighted means or averaging data from each animal neither altered the regression equation nor the correlation

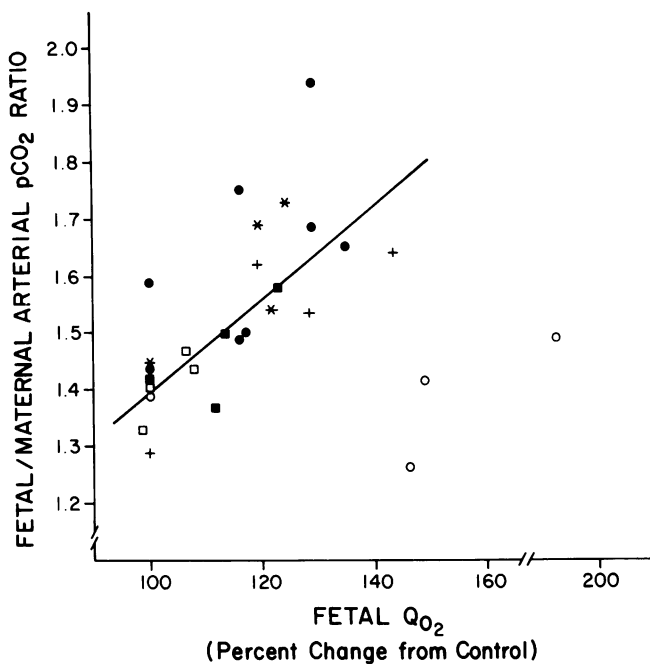


Figure 4. Relationship between Q_{O_2} expressed as percent of control and fetal/maternal arterial PCO_2 ratios. One animal (○) has been deleted from regression calculations. ($n = 24$, $y = 0.01x + 0.6$, $r = 0.69$, $P < 0.001$).

coefficient. Although a significant relationship ($P < 0.001$) was noted between the rise in fetal plasma glucose and the simultaneously sampled plasma insulin concentration (Fig. 5), no relationship was noted between fetal insulin concentrations and fetal Q_{O_2} before and during hyperglycemia. No changes in maternal glucose concentrations were observed during the experimental period.

Discussion

Previous work using the chronically catheterized fetal lamb model has demonstrated that chronic fetal hyperglycemia is associated with significant distal arterial hypoxemia and a mild arterial hypercapnea (4). With pronounced hyperglycemia, progressive hypoxia, metabolic acidosis, and fetal demise were evident. Although a linear relationship was apparent between the degree of hyperglycemia and the relative fall in fetal arterial O_2 content, the mechanism behind the fetal hypoxemia was unclear. Major hypotheses to explain these alterations included either stimulation of fetal and/or uteroplacental O_2 consumption or depression of transplacental O_2 transport due either to decreased O_2 diffusion or altered fetal hemoglobin- O_2 affinity.

The present data may be interpreted to indicate that the development of hyperglycemia in the fetal lamb induces an acceleration of the fetal metabolic rate and that the increase in

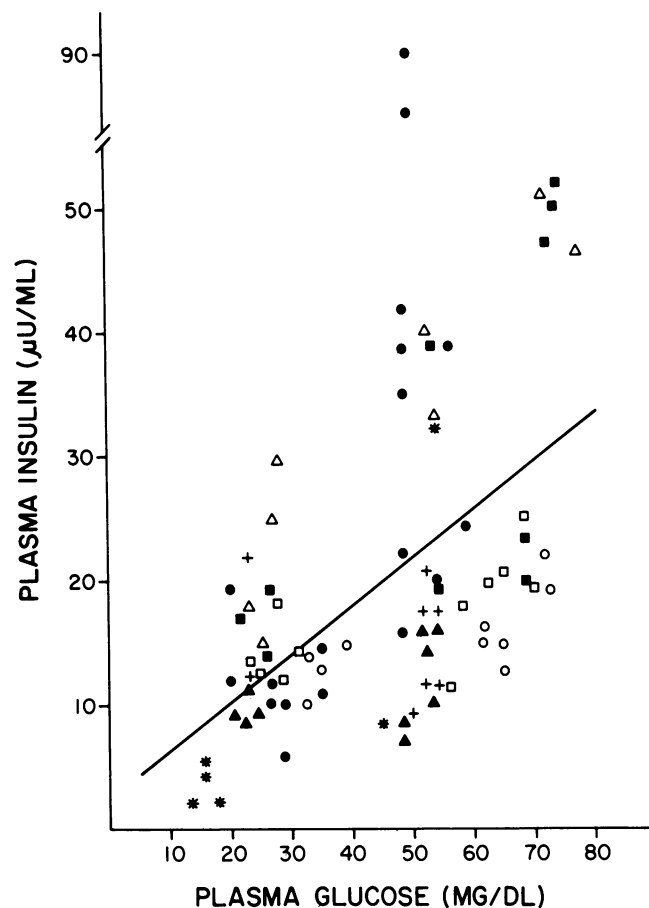


Figure 5. Relationship between fetal plasma glucose and insulin concentrations during control and experimental periods. Each symbol represents a different animal preparation. ($n = 83$, $r = 0.43$, $y = 0.39x + 2.24$, $P < 0.001$).

fetal O_2 consumption is almost wholly responsible for the observed fall in preplacental arterial O_2 content. Although hyperglycemia has been shown to alter hemoglobin- O_2 affinity in diabetic states (12), no changes in fetal hemoglobin- O_2 affinity or fetal erythrocyte 2,3-DPG concentrations were observed. In addition, no changes in monitored vascular parameters were noted to account for the above mentioned changes in fetal O_2 content.

In further studies using this model (13), concomitant increases in glucose and lactate uptake have been demonstrated during fetal hyperglycemia. It is of particular interest that significant increases in fetal glucose entry rate as well as fetal O_2 consumption occurred. Such accelerated oxidative metabolism would be expected to be accompanied by increased fetal CO_2 excretion. The small but significant elevation in preplacental arterial PCO_2 is suggestive evidence for accelerated CO_2 excretion since it is unlikely that transplacental CO_2 diffusion would be

significantly altered in the face of normal O₂ diffusion and stable umbilical and uterine blood flows (14, 15). From the theoretical model of transplacental CO₂ diffusion derived by Hill et al. (15), the observed rise of 3.8 to 4.4 torr in fetal arterial PCO₂ would be associated with a 20–30% increase in fetomaternal CO₂ transfer. The observed change in fetal arterial PCO₂ could not be accounted for by changes in maternal CO₂ tension, which were stable to decreased during the experimental period.

Some precedent exists to suggest that the fetal metabolic rate may be altered under experimental conditions. Lorijn and Longo (16, 17) have demonstrated significant stimulation of O₂ consumption in fetal lambs using direct fetal infusions of norepinephrine or triiodothyronine. In addition, other recent work (18, 19) suggests that acceleration of fetal oxidative metabolism may also occur during fetal insulin infusion. The increase was effected by widening of the umbilical venoarterial O₂ content difference without change in umbilical blood flow although significant increases in cardiac output occurred. In the insulin infusion studies, pharmacologic doses of insulin were used and fetal insulin concentrations were generally 2–20-fold above the range seen with the endogenous hyperinsulinemia observed in the present series of experiments. Since in the fetal state, alterations in cardiac output relate more to change in heart rate than stroke volume (20), the absence of significant fetal tachycardia in the chronically hyperglycemic fetal lamb suggests that little increases in cardiac output of the type seen with exogenous insulin infusion occurred. This finding, in addition to the lack of a significant relationship between fetal plasma insulin concentration and either the degree of arterial hypoxemia (4) or the rise in fetal O₂ consumption would suggest that the glucose-induced stimulation of fetal O₂ consumption may not be mediated by insulin. However, since the degree of fetal hyperinsulinemia produced was variable, a significant relationship between endogenous hyperinsulinemia and acceleration of fetal O₂ consumption may have been obscured.

Stimulation of fetal O₂ extraction as seen in the current work has been demonstrated in a variety of other studies dealing with nonhormonal alterations in fetal oxygenation, particularly as a response to states of altered O₂ availability. Increases in umbilical O₂ extraction have been observed as responses to umbilical vascular ischemia (21), fetal hemorrhage (22), maternal O₂ deprivation (23), or decreases in uterine blood flow (24) without concomitant alterations in umbilical blood flows unless hypoxemia was severe. Since neither blood flow nor maternal oxygenation were altered during fetal hyperglycemia, the exact stimulus for the increase in fetal oxygen extraction remains obscure.

At present, little information is available regarding the ability of excesses in substrate delivery to directly alter fetal O₂ consumption. However, significant information does exist in vivo experiments done in adults to indicate that the observed fetal response is not unusual. In the adult human, starvation and refeeding are associated with a fall and subsequent rise in O₂ consumption (25). In addition, ingestion of a carbohydrate

meal in fasting adults resulted in increases in both O₂ consumption and CO₂ excretion (26). Several other studies in adult humans supported with parenteral nutrition have tended to confirm the observation that substrate excess induces acceleration of metabolic rate. In studies utilizing parenteral infusions of glucose and amino acids with or without supplemental fat, significant enhancement of alveolar ventilation, O₂ consumption, and CO₂ excretion were noted when compared with control (27–29). In one case, these resultant increases were so great that they were detrimental to the patient under study (30).

No data are available at present to indicate the metabolic goal of increased fetal metabolism found in the present study. Using data derived by Battaglia et al. (31), the observed increase in fetal lamb O₂ consumption would amount to an increase of ~15 kcal/kg per d in caloric production. Even a doubling of the short-term fetal growth rate would not be expected to increase caloric expenditure beyond ~5 kcal/kg per d. In this regard, it is of interest to note that Rurak et al. (32) recently observed that normal fetal respiratory movements can account for up to 17% of the fetal O₂ consumption rate. Several authors (33, 34) have documented stimulation of fetal breathing by hyperglycemia in fetal lambs and humans, and thus, giving rise to the possibility that stimulation of muscular work may be in part responsible for the observed increases in fetal Q_{O₂}. Alternatively, it has been hypothesized (33) that these increases in fetal breathing movements are due to accelerated glucose-induced fetal CO₂ production with consequent respiratory center stimulation. Other possible mechanisms for a glucose-induced increase in fetal oxidative metabolism include excessive heat production (35), acceleration of fetal growth, and stimulation of futile cycling within some fetal tissues (36).

No direct information is available from human fetuses or infants of diabetic mothers (IDM's) to support the hypothesis that fetal hyperglycemia induces changes similar to those seen in fetal lambs. MacKay (37) noted a marked umbilical arterial hypoxemia in a small number of IDM's at delivery in the only study available in which O₂ content was measured in umbilical vessels. Naeye (38) noted that postmortem hepatic specimens of IDM's contained increases in extramedullary hematopoietic elements and suggested that this finding might be explained on the basis of an erythropoietic response to chronic fetal hypoxemia. Excesses in cord blood erythropoietin have been found in a number of IDM's (39). Since several investigators have demonstrated stimulation of fetal erythropoietin secretion induced by fetal hypoxemia (40, 41), particularly during fetal hyperglycemia, it is tempting to speculate that a number of clinical features found in human IDM's (late fetal demise, neonatal polycythemia, and neonatal hyperbilirubinemia) may be the result of hyperglycemia-induced increases in fetal Q_{O₂} and relative fetal arterial hypoxemia.

In summary, chronic glucose infusion in the fetal lamb induced a significant increase in fetal O₂ consumption within 24 h of the onset of hyperglycemia. The increase in O₂ consumption was linearly related to the degree of elevation in fetal plasma

glucose concentration. The increase in O₂ consumption was due to increased fetal O₂ extraction and not due to alterations in fetal blood O₂ affinity or in placental O₂ transport. No fetus became hypoxic as judged by the absence of significant metabolic acidosis. However, significant hypercapnea and respiratory acidosis were noted. The findings suggest that defined fetal glucose infusions induced stimulation of fetal oxidative metabolism but had little effect upon placental O₂ consumption.

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