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Arterial Hypoxemia and Hyperinsulinemia in the Chronically Hyperglycemic Fetal Lamb[30]

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Summary

Sustained fetal hyperglycemia was produced in eight chronically catheterized fetal lambs (seven twins, one singleton) by means of direct fetal glucose infusion. In twin preparations, only one twin was infused, the noninfused twin serving as a simultaneous *in utero* control. Glucose infusions lasted 7.6 ± 1.8 days and resulted in significant fetal hyperglycemia (from 20.3 ± 1.1 mg/dl to 58.2 ± 4.7 mg/dl, $P < 0.001$). The magnitude of the hyperglycemia was linearly related to the glucose infusion rate. Elevations of fetal plasma glucose and glucose infusion rate were associated with a significant fall in fetal arterial oxygen content ($P < 0.001$). In twin preparations studied, these relationships remained when the simultaneously sampled, noninfused twin was used as control. The fetal glucose-induced hypoxemia was not associated with fetal acidosis (tissue hypoxia) until the arterial oxygen content fell below 30% of baseline (mean base deficit in acidotic fetuses = 11.2 ± 2.2 meq/liter). Although Pa_{O_2} fell in hypoxemic fetuses (from 13.5 ± 1.2 mmHg to 9.7 ± 1.2 mmHg), the difference was not significant. Fetal plasma insulin rose during hyperglycemia from 10.2 ± 3.1 μU/ml to a peak concentration of 26.2 ± 3.3 μU/ml, but this response was blunted in markedly hypoxemic fetuses. Neither fetal anemia nor hemoconcentration were evident in these preparations to account for the fall in fetal oxygen content.

Speculation

Glucose-induced hypoxemia may be the result of accelerated fetal and/or uteroplacental oxygen consumption. *In utero* hypoxemia in the fetus of the pregnant diabetic may present a unifying hypothesis linking the known clinical findings of increased fetal red blood cell production, polycythemia, and late fetal demise in fetuses of diabetic mothers.

Macrosomia and hyperinsulinism are common features of the fetus of the diabetic mother (FDM), presumably stemming from chronic maternal hyperglycemia and excessive maternal-fetal glucose transfer (5, 19); however, the etiologies behind certain other features seen in the FDM, such as the increased incidences of venous polycythemia and late fetal demise (4, 11) are less evident. Experimentally induced fetal hyperglycemia has been associated with both fetal acidosis and fetal death (1, 22, 25). Some authors (5, 17) have suggested that chronic *in utero* fetal hypoxemia induced by maternal diabetes offers a unifying explanation linking excessive red blood cell production, fetal acidosis and excessive stillborn rates in this disorder; however, in at least one study, fetal lamb oxygenation during glucose infusion, as assessed by blood gas analysis, was normal despite the development of metabolic acidosis (22). With the aid of chronically catheterized singleton and twin fetal sheep, the effects of chronic isolated fetal hyperglycemia upon fetal oxygenation, insulin secretion, and fetal metabolism were explored. Because of the relatively steep oxyhemoglobin dissociation curve, fetal blood oxygen content was determined in addition to blood gas analysis to provide a better estimate of relative changes in oxygenation.

MATERIALS AND METHODS

Eight pregnant ewes were operated on between 115–125 days of gestation. Term gestation in the sheep is 147 days. Preoperatively, each ewe received intravenous sodium pentobarbital and spinal anesthesia (15 mg pontocaine). Polyvinyl catheters (internal diameter 0.034 inch) were placed in a fetal pedal or femoral artery and femoral vein as well as the maternal femoral artery for purposes of sampling and infusion. In the seven twin preparations, fetal arterial and venous catheters were implanted in both fetuses. All catheters were then tunneled subcutaneously to a pouch on the ewe's flank. Postoperative care and feeding were performed as described previously (10). No experiments were performed until after a postoperative recovery period of four days.

Experimental design. Details of the surgical preparations are given in Table 1. Four to five arterial blood samples were drawn from each fetus (from the singleton and both fetuses in each twin pair) over a two-day-control period and analyzed for plasma glucose and insulin concentrations, whole blood oxygen content, and blood gases (Po_2, Pco_2 and pH). In one twin preparation (animal #1), samples for oxygen content were not obtained. In selected experiments, fetal glucagon and lactate concentrations were also assessed. Maternal blood was withdrawn and sampled for plasma glucose, insulin concentrations, and blood gases. After the control period, the singleton fetus and one fetus in each of the twin preparations was begun on a continuous glucose infusion, utilizing the fetal venous catheter. Therefore, in the twin preparations, the noninfused twin served as a simultaneous *in utero* control. Chronic fetal glucose infusion was performed with variable drive, precalibrated syringe pumps. The ewes were housed in wooden carts with free access to water and food. In some cases the venous catheters were attached to a battery driven syringe pump by means of a wooden saddle and the ewes allowed to remain in a large pen in the University Animal Care Facility.

Glucose (35 or 50% glucose in sterile water) was delivered at rates between 5–20 mg glucose/kg estimated fetal weight/min. This resulted in volumes of administration to each fetus of between 0.5–2.5 ml/kg/h. In initial experiments, glucose infusions were begun at rates of 5–10 mg/kg/min and increased in a step-wise fashion every 3–4 days. In the last four preparations, however, no doses above 15 mg/kg/min were given. At delivery or autopsy, fetal weights were assessed. Glucose infusion rates were then recalculated on the basis of extrapolation from the delivery weight using fetal lamb growth charts for singletons and twins. At 1–2 day intervals after commencing the infusions, fetal and maternal blood samples were obtained to detect changes in oxygen content and glucose and insulin concentrations as well as significant acid base alterations. In selected cases, fetal lactate (four preparations) and glucagon (three preparations) concentrations were also monitored. Care was taken to minimize fetal blood sampling and to withdraw equal amounts from infused and noninfused fetuses in the seven twin preparations. Fetal hematocrit and total serum solid concentrations were also monitored daily to assure that glucose infusion and blood sampling did not result in significant anemia or hemodilution. In this study the term hypoxemia is used arbitrarily to indicate a fetal arterial blood oxygen content <50%

Table 1. *Surgical preparation*

Animal	Gestational age at surgery (days)	Duration of glucose infusion (days)	Twin or singleton	Birth weight infused/non-infused grams (ratio)	Outcome infused/noninfused
1	119	17	T	3184/2350 (1.35)	stillborn/liveborn
2	124	13	T	2915/3364 (0.87)	liveborn/liveborn
3	120	4	T	no weight available/2290	stillborn/liveborn
4	119	7	S	2699	liveborn
5	120	3	T	2200/1680 (1.31)	stillborn/stillborn
6	126	8	T	3235/3410 (0.95)	liveborn/intrapartum death
7	116	5	T	2910/2520 (1.15)	stillborn/stillborn
8	115	2	T		Catheters dislodged, ewe sacrificed

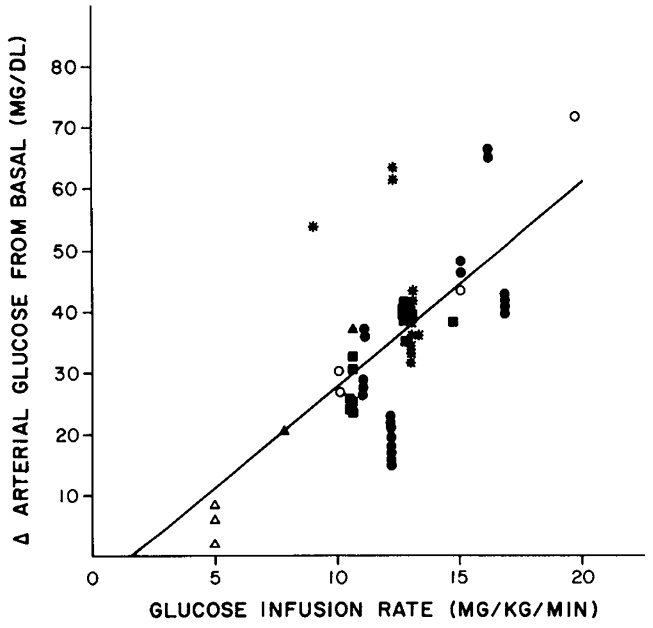

Fig. 1. Change in fetal plasma glucose concentration produced by varying the glucose infusion rate. Each symbol represents one preparation ($y = 7.02 + 3.40x$, $r = 0.71$, $P < 0.001$).

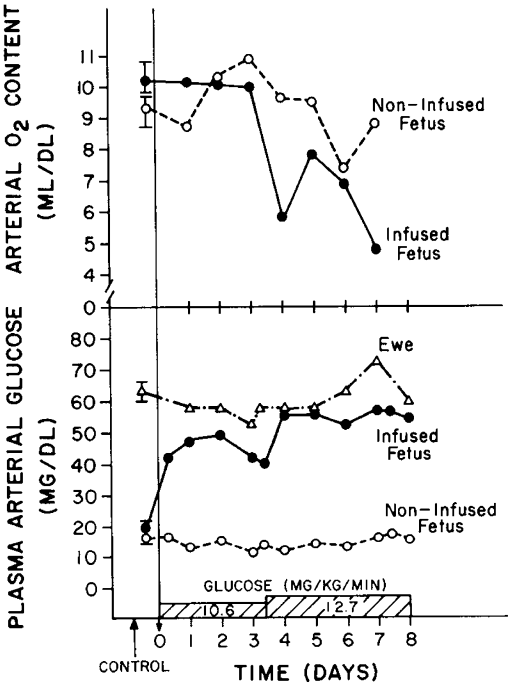

Fig. 2. Serial changes in plasma arterial glucose concentration and oxygen content in a representative twin preparation (No. 6).

of basal levels. The term acidosis is used arbitrarily to indicate a fetal arterial blood base deficit > 5 meq/liter. In both cases, these values fall outside of 2 S.D. from the mean control values obtained in the present studies.

Biochemical studies. Blood for glucose analysis was withdrawn into EDTA coated tubes, centrifuged and analyzed within 30 min for plasma glucose concentration utilizing the glucose analyzer glucose oxidase method (26). Whole blood oxygen content was determined using the Lex-O_2-Con (27) after withdrawing fetal blood into NaF-treated tubes. The Lex-O_2-Con was calibrated daily with distilled water saturated with oxygen at 0°C. Plasma lactate was determined using the enzymatic method of Olsen (18). Blood samples for insulin determination were withdrawn into chilled tubes containing 10 U heparin and then centrifuged. The supernatants were stored at −70°C until time of analysis. Insulin radioimmunoassay was performed using a modification (20) of the method of Morgan and Lazarow (16). Blood for glucagon assay was withdrawn into tubes containing a mixture of 10 U heparin/500 Kallikrein Inhibitory Units (K.I.U.). Trasylol (28) for each 1 ml sample and then centrifuged. The supernatant was stored at −70°C until time of assay. Glucagon radioimmunoassay was performed using Unger's technique (6) with the antibody 30K. A double antibody separation method (16) was used with goat anti-rabbit gamma globulin. Insulin and glucagon standards were supplied by Mary A. Root, Ph.D., Eli Lilly Laboratories, Indianapolis.

Statistical methods. Results are expressed as mean ± S.E. Statistical significance was assessed using the paired and unpaired Student's *t* tests. Linear and nonlinear regression analyses used the least squares method.

RESULTS

Glucose infusions lasted a mean of 7.6 ± 1.8 days with a range of 2–17 days (Table 1). Mean control plasma glucose was 20.3 ± 1.1 mg/dl. During the experimental period, plasma glucose concentration rose in the infused fetuses to 58.1 ± 4.7 mg/dl ($P < 0.001$). The magnitude of the increment of glucose concentration above basal was linearly related ($P < 0.001$) to the glucose infusion rate as shown in Figure 1. In the twin preparations, no changes in plasma glucose from control were noted in any of the noninfused twins during the experimental period.

Figure 2 depicts the changes in fetal plasma arterial glucose concentration and whole blood oxygen content in one representative twin preparation (animal #6). Although no significant

changes are apparent in glucose concentration of the ewe or noninfused fetus, the infused fetus exhibits a 2–3-fold rise in plasma glucose over the 8-day infusion period. Some variation is apparent in oxygen content of the noninfused fetus during both control and experimental period; however, the differences were not significant. In contrast, the hyperglycemic fetus exhibits significant decrements in arterial blood oxygen content, particularly at the higher rate of glucose administration. Blood gases were similar in both twins throughout the study and neither developed significant metabolic acidosis (base deficit > 5 meq/liter).

When data from infusion experiments were pooled, control fetal arterial oxygen content in the infused fetuses was 6.10 ± 0.99 ml/dl and fell to 3.71 ± 0.94 ml/dl ($P < 0.01$) during infusion. Noninfused fetuses had a mean arterial oxygen content of 6.2 ± 0.98 ml/dl in the experimental period, not significantly different from control. If the fetal arterial blood oxygen content in the experimental period is expressed as % of basal to normalize to a common reference standard, a significant nonlinear relationship ($P < 0.001$) between the fall in oxygen content in infused fetuses and the glucose infusion rate can be seen (Fig. 3A). If the simultaneously sampled noninfused twin is now utilized as the control for fetal oxygen content (Fig. 3B), a similar relationship is apparent; thus, a significant fall in the fraction of infused/noninfused fetal oxygen content is evident with increasing rates of glucose infusion. In neither relationship, however, was the fall in oxygen content statistically different from control until rates of glucose infusion above 10 mg/kg/min were utilized.

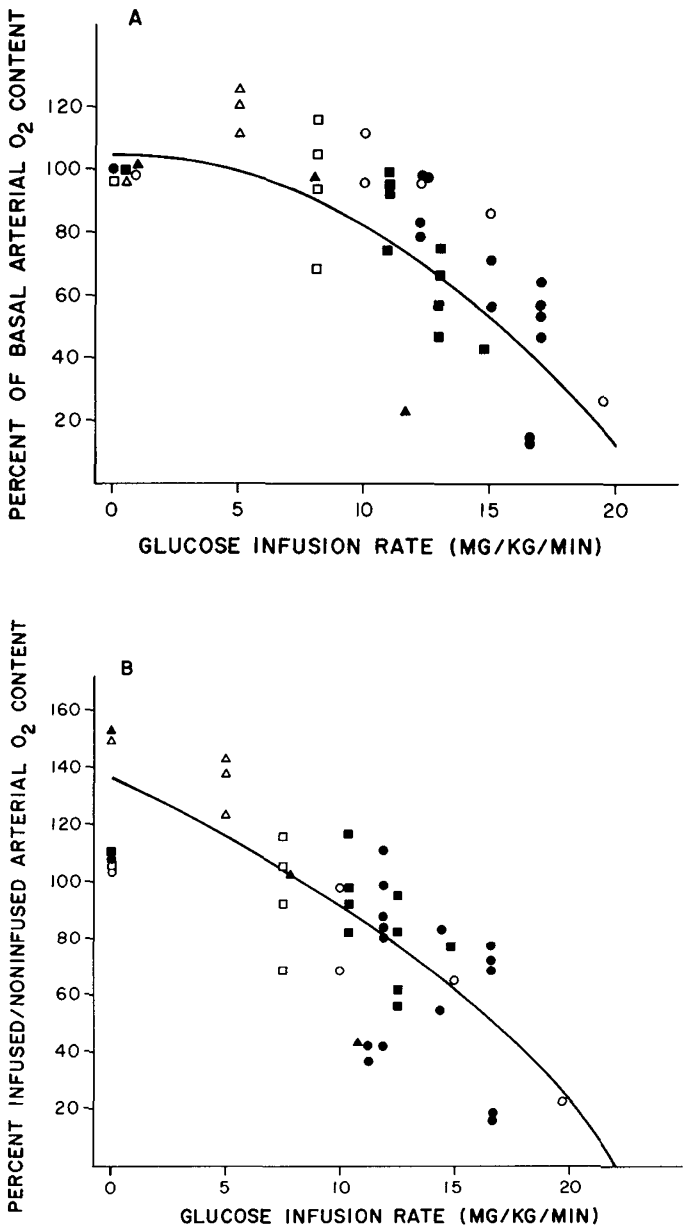

Fig. 3. Fetal arterial blood oxygen content relative to the rate of fetal glucose infusion in: (*A*), infused fetuses ($y = 103.68 + 0.10x - 0.23x^2$, $r = 0.60$, $P < 0.001$) and (*B*), twin preparations, with the noninfused twin serving as control ($y = 133 - 3.4x - 0.09x^2$, $r = 0.73$, $P < 0.001$).

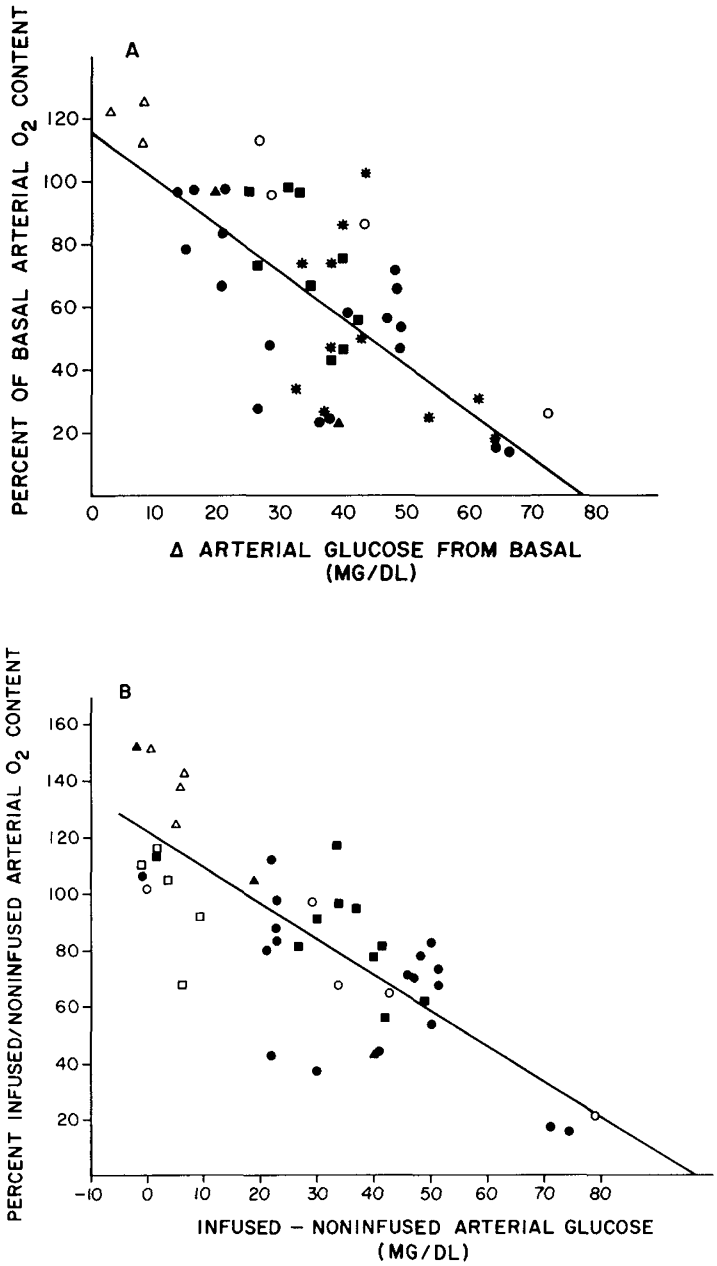

Fig. 4. Fetal arterial blood oxygen content compared to the increment in fetal plasma glucose concentration in: (*A*), infused fetuses ($y = 116.30 - 1.47x$, $r = 0.71$, $P < 0.001$) and (*B*), twin preparations, with the noninfused twin serving as a control ($y = 121.55 - 1.26x$, $r = 0.78$, $P < 0.001$).

The fall in fetal arterial oxygen content was also linearly related ($P < 0.001$) to the degree of hyperglycemia produced in the infused fetuses (Fig. 4A). A similar relationship is seen when the simultaneously sampled noninfused twin is used as the control for oxygen content (Fig. 4B).

Blood gas analyses are shown in Table 2. No significant changes were noted in pH or P_{O_2} by paired *t* test analyses although within each preparation there was a trend towards decreasing Pa_{O_2} with falling arterial oxygen content. In preparations that became hypoxemic (O_2 content < 50% basal) Pa_{O_2} fell from 13.5 ± 1.2 to 9.7 ± 1.2 mmHg. Due to interanimal variation, however, this differ-

ence was not significant. A small increase in P_{CO_2} ($P < 0.05$) was noted in the infused fetuses during glucose infusion. In three preparations (animals #2, 4, and 5, Table 1), discontinuance of infusion resulted in a return to normoglycemia and a rise in fetal arterial oxygen content. Four fetuses (animals #1–3, 5) developed significant metabolic acidosis (mean base deficit = 11.2 ± 2.2 meq/liter, pH = 7.09 ± 0.07) when the arterial oxygen content fell below 30% of basal. Three of the fetuses and one nonacidotic fetus (#7) died *in utero* but one acidotic fetus (#2) survived after discontinuance of the infusion.

Lactate was measured in four of the fetal preparations. In the infused fetuses, plasma lactate increased from 3.14 ± 0.25 to 5.96 ± 1.9 mM but this change was not significant by paired *t* test analysis. None of these fetuses became acidotic but two of the four had oxygen contents of <50% of basal during the infusion period.

Neither hematocrit nor total serum solids estimations changed from control values during the experimental period. Mean values for hematocrit and total serum solids in the twin preparations are shown in Table 3. No differences between control and experimental values among the infused twins, nor between infused and noninfused twins were seen in these studies using paired *t* test analysis.

Fetal plasma insulin concentration rose in response to fetal hyperglycemia from a control value of 10.2 ± 3.1 μU/ml to a peak concentration of 26.2 ± 3.3 μU/ml during glucose infusion. No significant changes in insulin concentration were noted in the mothers or in the simultaneously sampled noninfused fetuses in the twin preparations. In normoxemic infused fetuses, arbitrarily defined as having oxygen contents greater than 50% of basal, a significant relationship between fetal plasma glucose and fetal insulin (Fig. 5A, $P < 0.001$) can be seen. This response, however, was variable and the variability was not clearly related to changes in fetal plasma arterial glucose concentration, arterial oxygen content, or chronicity of infusion. As the fetuses become more hypoxemic, insulin concentration fell in spite of the hyperglycemic stimulus. In the five fetuses that developed arterial oxygen contents below 50% of basal (<2 S.D.'s below the mean, Fig. 5B), a relationship between glucose and insulin barely achieved statistical significance ($r = 0.34$, $P < 0.05$), but the slope of the equation (0.122) was half of that in Figure 5A (0.245). No relationship between plasma insulin and fall in arterial oxygen content was apparent. In addition, when insulin was introduced as a second variable into the relationship between the fall in oxygen content and degree of hyperglycemia in infused fetuses (Figure 4A and 4B), no enhancement of significance was found.

Mean plasma glucagon concentration in ewes and fetuses were 137 ± 31 and 121 ± 23 pg/ml, respectively. Fetal hyperglycemia had no effect upon glucagon concentration in the few animals studied, but a trend was evident toward increasing fetal glucagon concentration during marked hypoxemia. Fetal weights were obtained at birth or sacrifice in the singleton and in five of the twin pairs (Table 1). No significant differences were noted between infused and noninfused fetuses (2889 ± 185 *versus* 2665 ± 326 g, respectively; birthweight infused/noninfused ratio = 1.13 ± 0.10) although only three fetuses received infusions for greater than 7 days.

Table 2. *Fetal twin blood gases (six animals)*

	pH	P_{CO_2} (mmHg)	P_{O_2} (mmHg)
Infused fetus			
Control	7.40 ± 0.01	41.6 ± 0.8	13.5 ± 1.2
Experimental	7.38 ± 0.03	45.2 ± 1.8[1]	12.3 ± 1.0
Noninfused fetus			
Control	7.38 ± 0.02	43.9 ± 0.8	12.7 ± 1.3
Experimental	7.39 ± 0.02	44.7 ± 1.0	13.5 ± 1.3

[1] $P < 0.05$ different from control.

Table 3. *Twin glucose infusion*

	Preinfusion period		Last infusion day	
	Experimental twin	Control twin	Experimental twin	Control twin
Hematocrit (%)	36.2 ± 2.2	36.4 ± 2.0	35.4 ± 2.3	35.9 ± 2.5
Total serum solids (gm/dl)	4.7 ± 0.2	4.7 ± 0.2	4.8 ± 0.3	4.8 ± 0.3

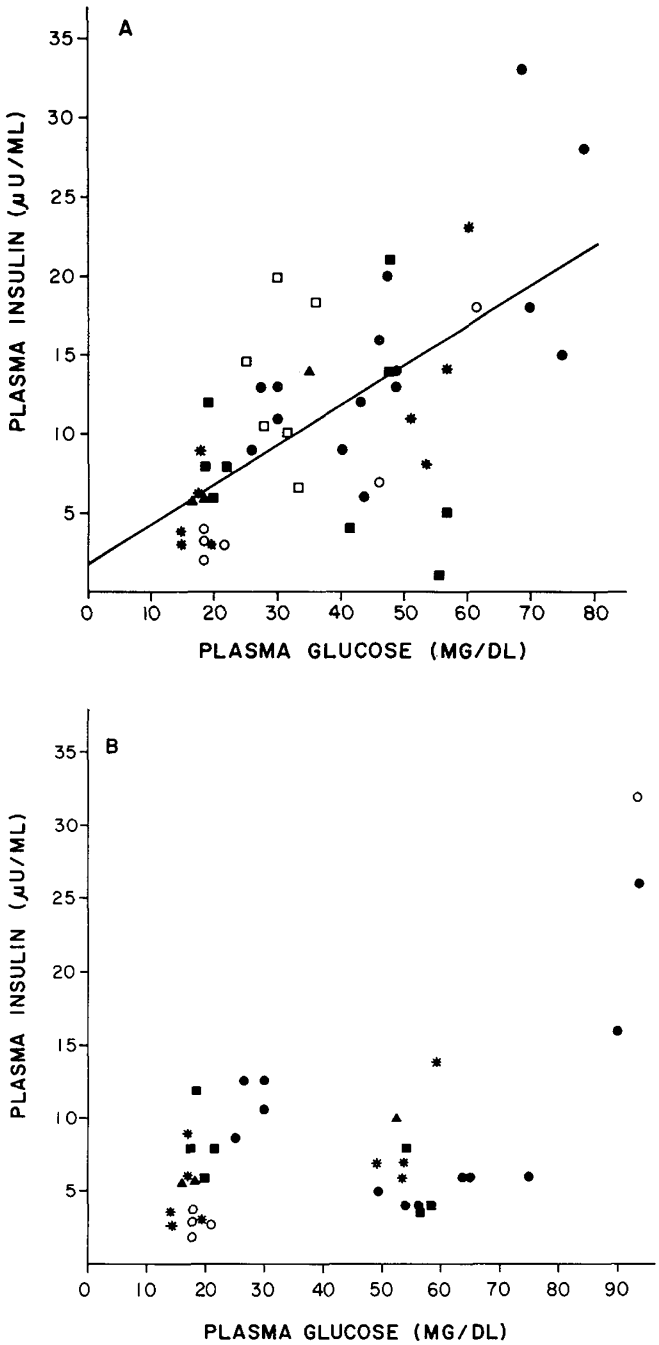

Fig. 5. Fetal plasma insulin concentration as a function of increasing fetal arterial plasma glucose concentration in: (*A*), normoxemic fetuses (arterial oxygen content > 50% of baseline (y = 1.91 + 0.25x, $r = 0.65$, $P < 0.001$) and (*B*), hypoxemic fetuses (arterial oxygen content < 50% of baseline) as contrasted with control values (y = 3.8 + 0.12x, $r = 0.34$, $P < .05$).

DISCUSSION

Experimentally induced fetal hyperglycemia has been associated with a variety of metabolic and hormonal consequences in the past. Particularly noteworthy have been increases in fetal plasma insulin and lactate concentrations after either maternal or fetal glucose infusion (1, 25). In addition, Fiser and coworkers (7), utilizing the chronically catheterized fetal sheep, noted an increase in fetal Po_2 and pH during a 2 h low-dose fetal glucose infusion. Bassett and Madill (1), however, using a similar preparation found that a more chronic fetal glucose infusion could induce not only fetal metabolic acidosis and hyperlactatemia, but fetal death. Robillard and coworkers (22) more recently substantiated this finding but could not detect significant alterations in fetal Pao_2 or $Paco_2$ despite fetal metabolic acidosis until the fetuses had marked hyperglycemia (>300 mg/dl). Shelley *et al.* (25) however, also using a fetal lamb model, could only induce fetal acidosis with glucose infusion in artificially hypoxemic fetuses. Thus, the relationship between fetal hyperglycemia, oxygenation, and acidosis has been unclear.

The results of chronic fetal hyperglycemia were assessed in this study with the aid of the chronically catheterized fetal sheep preparation. Because glucose concentration in the fetal sheep is approximately one-third of maternal, elevation of fetal glucose to 50–75 mg/dl would simulate maternal hyperglycemia. The results suggest that defined glucose infusions based upon fetal weight estimation, can result in reproducible and stable increases in fetal plasma glucose concentration. Fetal oxygenation was assessed by measurement of fetal arterial oxygen content in addition to Pao_2. Because fetal sheep hemoglobin has a relatively low P_{50} (approximately 15 mmHg), small changes in arterial Po_2 (which might be obscured by inter- and intraanimal variation) might reflect relatively large changes in actual fetal blood oxygen content (12). The results indicate a relatively early change in fetal oxygenation during experimentally induced hyperglycemia. Increases in the rate of glucose infusion and, thus, the degree of hyperglycemia produced, were associated with a decrement in fetal arterial oxygen content. The observations are consistent with the data of Robillard, *et al.* (22) that fetal arterial hypoxemia was not associated with acidosis (presumably secondary to tissue hypoxia) until marked hyperglycemia and hypoxemia occurred. Mean control distal Pao_2 from these fetal sheep preparations was somewhat lower than those reported by others (7, 22, 23). This discrepancy cannot be explained although the absence of acidosis and normal control arterial oxygen content (2.8 ± 0.4 mM) confirms the absence of fetal arterial hypoxemia before glucose administration. Although a trend was evident, fetal Pao_2 did not fall significantly during infusion, thus confirming the premise that oxygen content might be a better guide to subtle change in oxygen delivery. Tissue oxygenation in these preparations, however, was not assessed directly and the effects of the early changes in fetal oxygen content on tissue oxygenation are not known.

Fetal insulin secretion, although quantitatively and qualitatively different from the adult (20), does occur after an appropriate glucose stimulus in a variety of species (8, 15, 20). Hyperglycemia in the present preparations was generally associated with a modest but variable increase in plasma insulin concentration. Hypoxemia, stress, and acidosis are well known to cause significant blunting of pancreatic β cell responsivity to glucose in the adult and/or fetus (2, 21). Insulin concentrations were depressed in the hypoxemic fetuses even though a relatively larger glucose stimulus was present, indicating a subtle effect of hypoxemia on the fetal pancreas before other metabolic effects were evident.

Prolonged fetal glucose infusion resulted in an insignificant increase in blood lactate concentration similar to that found by Shelley *et al.* (25). Bassett and Madill (1) however, noted considerably larger alterations in fetal lactate concentration, particularly when fetal plasma glucose concentration was elevated above 60 mg/dl. Unfortunately, lactate concentrations were not measured in the preparations with severe hypoxemia. Although fetal lactate is, in part, placentally derived (3) under normal metabolic conditions, it is likely that the acidosis noted accompanying marked fetal hyperglycemia was related to lactic acid derived from fetal anaerobic metabolism secondary to tissue hypoxia.

The mechanism for the glucose-induced hypoxemia is unclear. An increase in oxygen consumption, either in the fetus and/or uterus-placenta, appears the most likely explanation. Because simultaneous measurements in the noninfused twins were uniformly associated with normal oxygenation and because in several experiments the acidosis was reversible, it is unlikely that instability of the surgical preparation played a role in causing fetal hypoxemia. Likewise, a fall in fetal oxygen carrying capacity due to fetal anemia is improbable. Inasmuch as umbilical venous oxygen content and umbilical blood flow were not measured in these experiments, changes in fetal oxygen consumption could not be monitored. Assuming that umbilical (fetal) blood flow remained normal until severe hypoxemia intervened (24), the fall in arterial oxygen content might represent increased fetal oxygen consumption, increased uteroplacental oxygen consumption and decreased fetal delivery or some combination of these two mechanisms (12, 13).

Lastly, fetal hyperinsulinemia has been shown to cause fetal arterial hypoxemia and elevation of oxygen consumption in the fetal sheep (4, 14). The mechanism behind this elevation is not known but may involve enhancement of mitochondrial respiration (9) as well as an increase in umbilical blood flow (14). Carson *et al.* (4) have suggested that *in utero* hypoxemia, if present in the FDM, may be the result of endogenous hyperinsulinemia. No relationship between fetal insulin concentration and decrement of oxygen content could be found in the present study. Although insulin may have contributed to the early hypoxemia produced during glucose infusion, the data indicate that, as in the adult, severe hypoxemia depresses insulin release in the fetus and that hyperinsulinemia was not a major factor in the development of fetal hypoxia or late fetal demise in these experiments.

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