Our ability to understand the physiology of the fetus in utero and the metabolic changes associated with pregnancy has increased in the last 10 years because of the development of fetal blood sampling techniques and the application of stable isotope methods.

The availability of techniques for sampling fetal cord blood in utero under ultrasonic guidance has made it possible to investigate the intrauterine environment of the human fetus under relatively undisturbed conditions (1). Several investigators have evaluated the respiratory gases and acid-base balance, the concentration and fetal-maternal relationships of nutrients, the endocrinology, and the hematology of the human fetus through gestation (1). Subsequently, fetal blood sampling has been extensively used in cases of intrauterine growth retardation (IUGR) for the assessment of fetal well-being (2,3). The results of fetal blood analysis have been compared with those of other noninvasive biophysical procedures to obtain a better understanding of the intrauterine conditions of fetuses with IUGR (4,5). We have recently proposed a classification of the clinical severity of fetal growth retardation that is based on the analysis of noninvasive biophysical indices, such as Doppler velocimetry of the umbilical artery and fetal heart rate pattern (6). According to this classification, fetuses are placed in group 1 if they have a normal pulsatility index of the umbilical artery and a normal fetal heart rate; group 2 fetuses have an increased pulsatility index of the umbilical artery and a normal fetal heart rate; fetuses in group 3 have an increased pulsatility index of the umbilical artery and an abnormal fetal heart rate. The evaluation of fetal respiratory gases and lactate concentration performed in utero at the time of fetal blood sampling has revealed significant differences in oxygenation and acid-base balance within the three groups, according to clinical severity. All fetuses in group 1 have normal oxygenation and blood lactate concentration. In group 2, fetal hypoxia and acidosis are uncommon, whereas most fetuses in group 3 have hypoxia and lactic acidemia (6).

At the same time, the use of stable isotopes, which is safe in human pregnancies,
allows investigation of the maternal disposal rate of nutrients (7–9). In addition, comparison of fetal and maternal enrichments of labeled compounds at the time of fetal blood sampling or cesarean delivery provides information on the transplacental passage of nutrients (10) as well as on fetal and placental nutrient metabolism (11,12).

Some of the results of the studies on nutrient supply in human fetal growth retardation are presented below.

**GLUCOSE**

Evaluation of maternal and fetal glucose concentrations in normal pregnancies at the time of fetal blood sampling has shown that umbilical venous glucose concentration decreases significantly with increasing gestational age (13). As maternal glucose concentration is fairly constant and independent of gestational age, the maternal-fetal glucose concentration difference increases significantly during human pregnancy (13). These results suggest that one of the mechanisms by which an increased placental transport of glucose is achieved in human pregnancies is by the development of an increasing maternal-fetal glucose gradient as gestation advances.

As in normal pregnancies, a significant linear relationship between fetal and maternal glucose concentrations is present in IUGR pregnancies (13,14) (Fig. 1). However, the evaluation of the maternal-fetal gradient shows that although there is no difference between the normal fetuses and the IUGR fetuses of group 1, there is a significant and progressive increase of the gradient in IUGR fetuses of groups 2 and 3.

![FIG. 1. Relationship between umbilical venous and maternal "arterial" glucose concentrations in growth-retarded fetuses. Fetal glucose concentration (mM) = 0.7 + 0.67 maternal concentration (mM); r² = .77; p < .001.](image-url)
NUTRIENT SUPPLY IN FETAL GROWTH RETARDATION

FIG. 2. Maternal-fetal glucose concentration difference in normal and growth-retarded pregnancies divided according to clinical severity (see text). AGA vs. group 1, NS; AGA vs. group 2, \( p < .01 \); AGA vs. group 3, \( p < .001 \).

(Fig. 2). Thus, as a consequence of the reduction in placental size, there is a significant reduction of fetal glucose concentration, which increases the transplacental glucose gradient. Figure 3 shows that in IUGR fetuses at the time of elective cesarean delivery, as the transplacental glucose gradient increases the umbilical uptake of glucose also increases. Thus, it is likely that this increase in gradient represents an adaptive mechanism by which the human fetus faces the restriction of placental size, thereby maintaining the glucose uptake. This hypothesis is further supported by experimental studies performed in the heat-exposed model of growth-retarded fetal lambs, where as a compensatory response to the decreased placental capacity for glucose transport, there is a decrease in fetal glucose concentration and a consequent increase in the transplacental glucose concentration difference, which increases the net flux of glucose from placenta to fetus by approximately 50% (15).

The importance of maintaining an adequate supply of glucose to the fetal compartment is further supported by a study performed with D-[U\(^{13}\text{C}\)]glucose infused in patients with pregnancies complicated by IUGR at the time of fetal blood sampling (11). No significant differences were detected between fetal and maternal glucose enrichments (0.47% ± 0.04 vs. 0.47% ± 0.03), with a mean fetal-maternal MPE (molar percent enrichment) ratio of 0.99 ± 0.01, not significantly different from 1. This implies that there is little if any glucogenesis within the fetus. Thus, transplacental transport represents the most important source of glucose for the growth-retarded fetus.
FIG. 3. Relationship between umbilical glucose/oxygen quotient and transplacental glucose gradient in growth-retarded pregnancies at the time of elective cesarean delivery. \( G/O_2 = -1.12 + 1.38 M^{\text{A}} - UA \text{ (mM)}; r^2 = .52; p < .001. \)

AMINO ACIDS

Many studies have shown that the concentration of fetal amino acids is significantly decreased in IUGR pregnancies, both at the time of fetal blood sampling (16,17) and at delivery (18,19). At cesarean delivery, the umbilical venoarterial difference of \( \alpha \)-amino nitrogen is significantly reduced in IUGR fetuses when compared with appropriate-for-gestational-age (AGA) fetuses (18). Given that umbilical blood flow is often reduced in these pregnancies, this would imply that the umbilical uptake of amino acids is also reduced.

In IUGR fetuses sampled \textit{in utero} as early as 26 weeks, the umbilical venous plasma concentration of the three branched-chain amino acids—leucine, valine, and isoleucine—is significantly reduced. This reduction is independent of the clinical severity of IUGR and might reflect the presence of an early alteration in the placental transport of amino acids (6). Studies on the system A amino acid transporter in the microvillus membrane of placentae of growth-retarded babies have shown that the activity is reduced compared with the placentae of AGA babies (20).

In a recent investigation in which 23 IUGR pregnancies were studied at the time of fetal blood sampling, we have shown that the fetomaternal concentration difference of most amino acids and of total \( \alpha \)-amino nitrogen is significantly reduced in IUGR (21) (Fig. 4). This difference is caused by a decrease in fetal and an increase in maternal amino acid concentrations. In IUGR mothers, the concentration of lysine,
FIG. 4. Umbilical venous-maternal “arterial” plasma concentration difference of total α-amino nitrogen in AGA and IUGR pregnancies divided according to clinical severity (see text). AGA vs. each IUGR group, p < .01.

histidine, valine, isoleucine, leucine, phenylalanine, arginine, alanine, and tyrosine is significantly increased when compared with AGA mothers. Total α-amino nitrogen is also significantly increased. In addition, for most amino acids there is a significant relationship between fetal and maternal concentrations, both in AGA and IUGR pregnancies. However, even though the plasma umbilical venous concentration of the individual amino acids does not differ significantly between AGA and IUGR, the relationship between fetal and maternal concentrations is significantly different in IUGR; the relationship between umbilical venous and maternal leucine concentrations is shown, as an example, in Fig. 5. No significant differences are present among the three groups of IUGR pregnancies as far as the maternal-fetal amino acid relationships are concerned. Thus, the decrease in fetal concentrations and in the fetomaternal concentration difference is independent of subgroups and therefore—within these limits—of fetal oxygenation and perfusion.

SUMMARY

IUGR complicates approximately 4% to 10% of deliveries and represents an important cause of perinatal morbidity and mortality (22). At present, no intrauterine treatment is available, and clinical management relies on the choice of the best timing of delivery. However, in growth-retarded pregnancies there are fetal as well as maternal metabolic differences in comparison with normal pregnancies. It is possible to speculate that the intrauterine detection of such derangements might be used
FIG. 5. Relationship between umbilical venous and maternal "arterial" plasma concentrations of leucine in AGA ($y = 57 + 0.8x; r^2 = .60; p < .001$) and IUGR ($y = 50.4 + 0.6x; r^2 = .25; p < .01$) pregnancies.

in defining new nutritional therapeutic strategies in these pregnancies, according to clinical severity.

REFERENCES


**DISCUSSION**

**Dr. Soothill:** I noticed that some of your babies had an oxygen content less than 2 mmol/l, in fact less than 1 mmol/l in some cases, and that is amazingly hypoxic for a baby with normal Doppler. Could you comment?

**Dr. Nicolaides:** Those data also included the AGA babies.

**Dr. Marconi:** Those were data at cesarean section. We think that the reason why we have increased lactate concentration differences in AGA and IUGR of group 1 is that in cesarean section there is an acute stress.

**Dr. Battaglia:** Statistically, perhaps, some of the analyses from groups 2 and 3 might have been the same, but in fact when you look at the data, it is group 3 that is really different. So it seems that it is for group 2 that we need new ways of assessing those babies, because in group 2 there are a few babies that look as bad as in group 3, but most of them don’t. So using this crude classification isn’t enough. This is the group in which we need better tools to sort out the infants who in a few days are going to be in group 3. That is where the problem is clinically. I think we need new methods there.

**Dr. Herrera:** Could NMR (nuclear magnetic resonance) spectrometry be the solution to this question?

**Dr. Soothill:** In UCL, they are trying to use NMR to assess the oxygen concentration in the fetal brain, but you have to paralyze the fetus because of movement artifact. But this is for the future.
Unidentified questioner: Would you care to speculate on the reason why it appears that the maternal amino acid concentrations are elevated?

Dr. Marconi: I guess it is a maladaptation to pregnancy, probably mediated through some hormonal mechanism. We now have evidence of many differences in these mothers. We have found an increase in triglycerides, amino acids, and lactate, so we can call it a maladaptation to pregnancy, but we don't know yet what the mediator of this situation is.

Dr. Nicolaides: One explanation for the high amino acids in the mother is hemoconcentration because of the reduced maternal blood volume in IUGR.

Dr. Marconi: IUGR mothers are not always hemoconcentrated.

Dr. Nicolaides: Have you any explanations for the high fetal nonessential amino acids? We found that essential amino acids are down in the fetus and the nonessentials are up, except serine, which behaves like an essential amino acid.

Dr. Marconi: In our experience, the concentration of nonessential amino acids is also reduced in the IUGR fetus, even though the concentration only of serine and tyrosine is significantly lower when compared with AGA. This observation is in agreement with in vitro studies of placental amino acid uptake in AGA and IUGR pregnancies.