Maternal Hypoglycemia As Potential Cause of Fetal Injury: Some Theoretic Considerations

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The concept that maternal hypoglycemia may have deleterious effects on the fetus has been based on the clinical observation of lowered birth weights of these infants and lowered I.Q. and motor scores of infants of mothers with ketonuria(1). An increase in perinatal mortality has been also reported among hypoglycemic mothers who have evidenced lower than expected excretion of estriol (2). The concern about possible adverse effects of maternal hypoglycemia on fetal development has been increasing as the contemporary management of diabetes mellitus in pregnancy, calls for a rigid maintenance of maternal blood sugar in the euglycemic range. The purpose of this presentation is to review the mechanisms by which maternal and hence fetal hypoglycemia could be adverse to fetal development.

In the fetus, glucose is the main source of energy for metabolic processes and the principle precursor of neutral fats and glycogen. It can be calculated that between the 35th and 40th week of gestation when fat deposition is at its maximum, the total glucose utilization per kilogram of fetal body mass is about 8 mg per minute. Assuming a placental utilization of glucose of 7-8 mg per minute, and an intervillous space and villous capillary flow rates of 150 ml per kilogram of fetal mass per minute, the concentration difference between uterine artery and umbilical artery is 12 mg%. Such calculations are in close agreement with actual measurements of fetal and maternal glucose concentration during labor (e.g. 72mg% and 82 mg% respectively)(3). There are no data available in the human regarding the concentration of dextrose in fetal blood necessary to maintain fetal functions within limits of norm. Typically during the second to ninth hour of postnatal age, the mean value of plasma glucose is about 50 mg%, which is about 20 mg% less than that observed in fetuses of euglycemic mothers(4). During the first three (3) days postnatally, as many as five (5%) percent of apparently normal newborns have plasma glucose concentrations of less than 35 mg%, without exhibiting clinical signs of hypoglycemia(4).

Assuming that the tolerance of the fetus to hypoglycemia is not less than that of the newborn, it can be projected that adequate supply of glucose to the fetus would be ensured as long as maternal arterial glucose concentration exceeds 47 mg%. This value has been derived by adding to the low normal neonatal glucose values, the calculated difference between glucose concentration in the uterine artery and in the umbilical artery. Most individuals are overtly syptomatic at plasma glucose concentrations below 50 mg%; hence it is unlikely that such relative states of maternal hypoglycemia, at least in the wakeful state, would remain undetected.

From the above considerations, it can be inferred that fetal glucose concentration in the asymptomatic mother is substantially above that required to meet fetal metabolic needs, and that sub-

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strate deprivation is not a likely cause of adverse sequelae to the fetus. The impact of severe maternal hypoglycemia as might occur with transient maternal hyperinsulinemia is expected to be attenuated due to the ability of the fetus to mobilize its own glycogen stores.

If it is agreed that fetal hypoglycemia is unlikely through its direct effect to elicit deleterious consequences, several of its indirect actions deserve close scrutiny as causative factors. They are: ketonemia, hypoinsulinemia, and increased release of catecholamines from maternal stores.

Maternal ketonemia has been associated with lowering of neurologic and intellectual functions in the offsprings irrespective of the underlying condition and the maternal blood sugar level(1). These data have been generally interpreted as supportive of the contention that maternal and hence fetal ketonemia adversely effect the development of the central nervous system. More recent data have, however, challanged the validity of this interpretation. It has been demonstrated that endogenous ketones are readily oxydized by brain tissue of the fetus and, at least theoretically they represent as suitable a source of energy as glucose (5). We propose that ketonemia is an associated variable in the causation of neurologic injury, the primary being hypoxia caused by impaired perfusion of the uterus, occuring as a result of the maternal state resulting in ketonemia.

Due to the well recognized role of insulin in fetal growth, hypoinsulinemia, which is likely to result from fetal hypoglycemia, may play an important role in alterating the normal growth pattern of the fetus. In contrast to the previously held view that insulin exerted its effect only on the adipocytes, it is now known that insulin can differentially affect various fetal organs and their sizes(6). Although certain amino acids can increase the release of insulin from fetal pancreas, it is proposed that low glucose levels of the fetus would lead to relative hypoinsulinemia with the resultant reduction of somatic growth and subnormal accumulation of neutral fats and glycogen(7).

Such newborns, although normocephalic, would be classified as low birth weight, and would experience in the neonatal period a number of difficulties such as hypothermia and hypoglycemia. The clinical findings of such newborns are explained on the basis of high thermal conductance due to absence of insulation by subcutaneous fat, increase in energy transformation rates through hemothermal mechanisms, and low glycogen content of the liver.

Maternal hypoglycemia causes activation of the adrenergic nervous system resulting in both norepinephrine and epinephrine release. It has been demonstrated that in patients with diabetes mellitus, hypoglycemia doubles the plasma concentration of norepinephrine(8). Exogenous as well as indogenous norepinephrine causes marked reduction in fetal oxygenation secondary to alpha adrenergically mediated vasoconstriction in the vasculature supplying the uterus. A similar effect has also been noted following ad-

ministration of epinephrine(9). A chronic or intermittant reduction in intervillous space perfusion could lead to a picture of partial prolonged fetal hypoxia without hypercarbia or acidosis.

We conclude that fetal hypoglycemia and ketonemia per se, resulting from maternal hypoglycemia, is unlikely to have an adverse effect on fetal development in man. Impaired neurologic performance of children born to hypoglycemia and ketonemic mothers is more likely to be brought about by impaired fetal oxygenation secondary to adrenergically mediated vasoconstriction in uterine circulation. More subtle aberrations from normal development, and reduction in birth weight of these infants could be accounted for by hypoinsulinemia of the fetus. The role of other substances that might be present in abnormal concentrations in fetuses of hypoglycemic mothers, such as glucagon or growth hormone, still remains to be elucidated.

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