These infants are remarkable not only because, like fetal versions of Shadrach, Meshach and Abednego, they emerge at least alive from within the fiery metabolic furnace of diabetes mellitus, but because they resemble one another so closely that they might well be related. They are plump, sleek, liberally coated with vernix caseosa, full-faced and plethoric. The umbilical cord and the placenta share in the gigantism. During their first 24 or more extra-uterine hours they lie on their backs, bloated and flushed, their legs flexed and abducted, their lightly closed hands on each side of the head, the abdomen prominent and their respiration sighing. They convey a distinct impression of having had such a surfeit of both food and fluid pressed upon them by an insistent hostess that they desire only peace so that they may recover from their excesses. And on the second day their resentment of the slightest noise improves the analogy while their trembling anxiety seems to speak of intra-uterine indiscretions of which we know nothing.

Thus Farquhar described the newly born infant of the diabetic mother. The purpose of this presentation is to review the information that is available concerning such infants and their difficulties. Dekaban and Baird, comparing 235 pregnancies in 48 diabetic mothers with 249 in paired nondiabetic controls, not only reaffirmed the increased intrauterine and neonatal mortality among these infants but also demonstrated an increased morbidity among the survivors. This morbidity included congenital malformations, retardation of development and epilepsy. Despite the increased morbidity and mortality, many of these infants are not sick and do well.

Recent reviewers have emphasized the maternal factors that can and cannot be correlated with illness in the infant. Among the latter are duration of diabetes, insulin requirements, age, parity, toxemia of pregnancy, type of anesthesia and the mode of delivery. The administration of hormones, estrogen and progesterone to the mother does not influence the fate of the infant. On the other hand, the severity of the diabetes as well as the control during pregnancy and at the time of delivery can be equated with survival. Bleeding during pregnancy, the development of polyhydramnios, induction or delivery before 33 weeks or after 38 weeks gestation are all associated with increased infant morbidity and mortality.

Once the infant is born, his condition at birth (58% mortality, with an Apgar score of 0-3, compared to 10% with score of 10), birth weight, sex and the presence of congenital abnormalities all influence his survival. However, even as important as the infant who has difficulty is the large group of babies, varying from 50 to 65% of live-born infants who have an uneventful clinical course. These relatively well babies, if included with the sick infants of diabetic mothers, may obscure the value of any specific therapy as well as the significance of abnormal laboratory observations. As an example, although there were no significant differences in the mean hyperglycemic responses to glucagon between infants of nondiabetic mothers and infants of diabetic mothers, the 14 sick infants in the latter group showed less of a hyperglycemic response than did the 18 well infants. As far as the authors are aware, no significance has been attached to these findings.
as calcium levels are concerned, the mean for 22 offspring of diabetic mothers was 8.2 mg/100 ml, yet the mean for 9 infants in the group with a stormy course was 7.1/100 ml. Therefore, it is important to avoid generalizations concerning the metabolism of all infants of diabetic mothers as well as their response to specific therapy.

Regarding therapy, all agree that good diabetic control, early hospitalization of the mother, delivery between 35 and 37 weeks gestation, and experienced, gentle and prompt resuscitation of the infant, are all important in reducing mortality. The areas of controversy include the benefit of gastric suction, early feeding, glucose, saline and bicarbonate solutions given parenterally, the maintaining of normoglycemia and normocalcemia, digitalis, cortisone, oxygen and antibiotics. The manifestation of illness in these infants consists of respiratory distress, edema, spells of apnea, jitteriness or spasm, and the hyaline membrane syndrome. The problems of impending heart failure, anoxia, pulmonary, cerebral or cardiac edema and infection, as well as hypocalcemia, hypoglycemia, respiratory and metabolic acidosis, and cortisone withdrawal have each and all been incriminated as etiologic factors. A controlled study alternating a specific therapy in sick infants of diabetic mothers with a follow-up sufficiently long to determine morbidity is needed before there can be any definitive conclusion. Despite the fact that over 4,000 pregnancies in diabetic women have been reported, their infants still present many unsolved problems. The majority are well; yet many have biochemical hypoglycemia (42% of 213) and some, hypocalcemia. The sick infants have respiratory distress and die of hyaline membrane disease. The need for distinguishing between sick and well babies of diabetic mothers is obvious and requires emphasis in avoiding generalizations concerning the metabolism and therapy in these infants.

**DISCUSSION**

**Dr. Laskers:** Do you have any opinion about babies of prediabetic mothers?

**Dr. Cornblath:** Most data would indicate that the offspring of prediabetic mothers are excessively large, have an increased incidence of respiratory distress and hyaline disease, and an increased morbidity and perinatal mortality. The only exceptions to this are the findings in Boston, where informal reports would indicate that the infants are of excessive size but have no increase in perinatal morbidity or mortality.

**Dr. Robert E. Cook:** What influence does diabetes in the father have in the infant?

**Dr. Cornblath:** In a report from South Africa, the infants of diabetic fathers were found to be significantly larger than infants born to parents, neither of whom have diabetes. However, these larger infants did not have any increase in perinatal difficulties. In another report from the Netherlands, however, the infants of diabetic fathers were found not to be larger nor have any other difficulty that would distinguish them from infants of normal fathers. More data are necessary before any definite conclusions can be drawn.

**Dr. Calvin:** Have there been any vascular abnormalities noted in the newborn infants of diabetic mothers?

**Dr. Cornblath:** I know of no studies in which the conjunctival vessels in the eye of the newborn have been looked at with this in mind. Ditzel (Diabetes, 3:99, 1954) described an increased incidence of abnormalities in bulbar conjunctival blood vessels in 75 children of diabetic mothers when compared to 75 children of normal mothers. These vascular abnormalities were present prior to the onset of clinical diabetes. Your suggestion that these be studied in newborn infants might be a fascinating one and very important.

**Visiting Physician:** What is the incidence and significance of the hypoglycemia in these infants, if any?

**Dr. Cornblath:** Before discussing the significance of the hypoglycemia in these infants, there is a question in the literature whether, indeed, hypoglycemia exists in the infants of diabetic mothers. Except in those studies where total reducing substances or isolated blood sugars were obtained, there seems to be no question that a larger number of infants of diabetic mothers have true blood sugar levels below 30 mg/100 ml than do normal infants. Therefore, there is an increased incidence of hypoglycemia in these babies. The more difficult question is: "Does this hypoglycemia have any significance?" At one time it was believed that all the difficulties these babies experienced was due to hypoglycemia. Now the pendulum has swung, and most people report that none of the difficulties these infants have is due to hypoglycemia. Personally, I would think that the answer probably lies somewhere between these two extremes.
18:199, 1955) have reported an incidence of hypoglycemia associated with symptoms in about 5 of 83 newborns studied. It should be emphasized that the symptoms and signs of hypoglycemia in the newborn may consist of apnea, cyanosis, limpness, failure to suck, absent moro reflex, listlessness, wilting spells, convulsions or coma.

In addition to the symptoms caused by hypoglycemia, there are several theoretical considerations that would indicate that providing substrate (glucose) for the brain might be important in preventing neonatal as well as subsequent morbidity in offspring of diabetic mothers. In the newborn animal, hypoglycemia produced by insulin or glycolytic poisons shortens the newborn animal’s survival in nitrogen. In human adults receiving insulin shock therapy, there is a decreased oxygen uptake by the brain as the blood sugar concentrations decrease below 20 to 25 mg/100 ml, indicating that the brain cannot function when substrate is not present. For these reasons it would appear desirable to maintain a blood sugar concentration of around 30 to 40 mg/100 ml, which is normal for the newborn infants of diabetic mothers. Sometimes this is difficult to do by giving glucose orally or parenterally. We have found that glucagon in amounts of 300 μg/kg is effective in increasing the blood sugar concentration and maintaining it in this range.

To date we have administered glucagon to over 40 offspring of diabetic mothers, with no untoward reactions. Unfortunately, patients have not been alternated, and there have not been sufficiently long follow-ups to permit proper evaluation of this hormone as a therapeutic agent. It certainly would be necessary to alternate a large number of sick infants of diabetic mothers with and without glucagon before any definitive recommendations can be made.

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CLINICAL CONFERENCE: INFANTS OF DIABETIC MOTHERS
Marvin Cornblath
*Pediatrics* 1961;28;1024

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