Malformations in Infants of Diabetic Mothers Occur Before the Seventh Gestational Week

Implications for Treatment

JAMES L. MILLS, LESTER BAKER, AND ALLEN S. GOLDMAN

SUMMARY

In the present study we used a developmental morphologic approach to fix the latest time in development at which the malformations commonly reported in infants of diabetic mothers could occur. Developmental morphologic dating shows that the significantly more common congenital malformations in infants of diabetic mothers occur before the seventh week of gestation. This suggests that any therapeutic intervention aimed at decreasing the incidence of congenital malformations must be instituted during the critical early period. DIABETES 28:292–293, April 1979.

It is now generally accepted that infants of diabetic mothers have a higher incidence of congenital anomalies[1–4] in general and of the caudal regression syndrome (agenesis or hypoplasia of the femorae and agenesis of the lower vertebrae) in particular. Improved prenatal diabetic management and neonatal care has reduced fetal wastage and death from respiratory disease.[2,5] Despite this improvement, the incidence of congenital malformations has not decreased over the past 25 yr.[6] Moreover, congenital malformations have now replaced respiratory distress syndrome as the most common cause of death in one series of infants of diabetic mothers.[6] These findings have added impetus to the search for an understanding of the teratogenic mechanism in the offspring of the diabetic mother.

METHODS

Kučera[7] reviewed the incidence of congenital malformations in the infants of diabetic mothers in 48 published papers covering the period from 1930 through 1964. He found 340 malformations in 7101 infants (4.8%). These were compared with the worldwide survey of congenital malformations taken by the World Health Organization, covering 431,764 infants and 7124 congenital malformations (1.65%). In the present report, the incidence of malformations in each of Kučera's specific categories was compared with that of the control population by use of the chi-square test to judge significance. Each category that was significantly different from that of the control population was then analyzed to determine the ratio of incidences, so that the relative increased frequency in infants of diabetic mothers could be shown.

In addition, those malformations that were determined to be significantly more frequent in infants of diabetic mothers were examined by a developmental morphologic approach.[8,9] This method is based on the knowledge of when organ development occurs and on the assumption that malformations of an organ cannot occur after the organ has been completely differentiated. Thus, for each anomaly, a time was assigned before which the defect must have occurred.

RESULTS

Table 1 shows the malformations found significantly more frequently in infants of diabetic mothers along with the ratio of incidences when compared with that of controls. The latest gestational age at which each of these malformations could have occurred is listed.

As illustrated, most anomalies occur sometime before the fourth to seventh weeks of gestation. This relatively brief period, early in pregnancy, is the critical time of teratogenesis.

DISCUSSION

The cause of the congenital malformations seen in infants of diabetic mothers has not been determined. Various aspects of the disturbed metabolic state in the diabetic mother have been suggested as possible teratogenic agents, including hyperglycemia, hypoglycemia, vascular disease, and other associated metabolic derangements.[2,3,10,11]

The present report cannot be used to determine which of the putative teratogenic agents associated with maternal diabetes is the actual cause. These observations can be used, however, to rule out insulin as the likely teratogen

From the Departments of Pediatrics and Pharmacology and the Robert Wood Johnson Clinical Scholars Program, University of Pennsylvania School of Medicine, Philadelphia, and Children's Hospital of Philadelphia.

Accepted for publication 28 December 1978.

TABLE 1
Congenital malformations in infants of diabetic mothers

Anomaly	Ratio of incidences*	Gestational age after ovulation[8,21,22] in weeks
Caudal Regression	252	3
Spina Bifida, Hydrocephalus, or other CNS defect	2	4
Anencephalus	3	4
Heart Anomalies	4	
Transposition of great vessels		5
Ventricular septal defect		6
Atrial septal defect		6
Anal/Rectal Atresia	3	6
Renal Anomalies	5	
Agenesis	6	5
Cystic kidney	4	5
Ureter duplex	23	5
Situs Inversus	84	4

* This ratio is derived from Kucera's[7] equation:

$$\frac{\text{Number of cases of this anomaly in diabetic group} \div \text{total diabetic group}}{\text{Number of cases of this anomaly in control group} \div \text{total control group}}$$

and to indicate the timing of any future, intervention studies.

The possibility that insulin itself may be responsible for the malformations seen in infants of the diabetic mother has received recurrent attention. This derives from animal work, in which congenital abnormalities were produced by insulin in chicken,[12,13] rabbits,[14] mice,[15] and rats.[16] However, all available evidence suggests that the human fetus is not exposed to insulin during the critical period. Like and Orci[17] found differentiated B-cells at about 10.5 wk gestational age, while Steinke and Driscoll[18] reported demonstrable insulin in the pancreas at around the eighth week of gestation. Fetal insulin secretion, therefore, does not occur until well after the critical period for teratogenesis. Similarly, the fetus does not appear to be exposed to maternal insulin. The placenta has been shown to be an effective barrier against maternal insulin, as demonstrated by the administration of radioiodinated hormone to the mother. In 16-wk to 20-wk fetuses studied at abortion[19] and in term infants,[20] insulin levels in the umbilical vein were, essentially, zero despite high levels in the maternal circulation. These combined observations would indicate, therefore, that the congenital malformations seen in the diabetic mother cannot be attributed to fetal exposure to insulin.

The present observations demonstrate that the insult causing the malformations in the infants of diabetic mothers occurs before the seventh week. This presumably relates to some aspect of the maternal milieu that is disturbed in diabetes. Thus, if better management of maternal diabetes can decrease congenital malformations, it is clear that it must be implemented in the crucial first seven weeks. This may require careful monitoring of all diabetic women of childbearing age, including education before pregnancy occurs, rapid diagnosis of pregnancy, and skillful diabetic management during the first two months of gestation, a time when most women with diabetes are not currently under medical supervision.

ACKNOWLEDGMENTS

The authors are grateful to Ms. Eileen Quinn for her assistance in preparing this manuscript.

The work was supported in part by NIH grants AM-13518, HDO-7107, and DE-4622, and a National Foundation-March of Dimes grant.

REFERENCES

[1] Yssing, M.: Long-term prognosis of children born to mothers diabetic when pregnant. *In* Early Diabetes in Early Life. New York, Academic Press, 1975, p. 575.

[2] Soler, N., Walsh, C., and Malins, J.: Congenital malformations in infants of diabetic mothers. Q. J. Med. *178*:303–13, 1976.

[3] Molsted-Pedersen, L., Tygstrup, I., and Pedersen, J.: Congenital malformations in newborn infants of diabetic women. Lancet *1*:1124–26, 1964.

[4] Heinonen, O. P., Slone, D., Shapiro, S., Gaetano, L. F. et al.: Birth Defects and Drugs in Pregnancy. Littleton, Mass., Publishing Science Group, 1977.

[5] Pedersen, J., Molsted-Pedersen, L., and Andersen, B.: Assessors of fetal perinatal mortality in diabetic pregnancy. Diabetes *23*:302–05, 1974.

[6] Soler, N. G.: Perinatal Medicine. Stockholm, Fifth European Congress of Perinatology, 1976, p. 108.

[7] Kučera, J.: Rate and type of congenital anomalies among offspring of diabetic women. J. Reprod. Med. *7*:61–70, 1971.

[8] Smith, D.: Recognizable Patterns of Human Malformation: Genetic, Embryologic and Clinical Aspects. Philadelphia, W. B. Saunders, 1970.

[9] Schwalbe, E.: Die Morphologie Der Missbilden Des Menschen und die Tiere. Jena, Gustav Fischer, 1906.

[10] Karlsson, K., and Kjellmer, I.: The outcome of diabetic pregnancies in relation to the mother's blood sugar level. Am. J. Obstet. Gynecol. *112*: 213–20, 1972.

[11] Day, R., and Insley, J.: Maternal diabetes mellitus and congenital malformation. Arch. Dis. Child. *51*:935–38, 1976.

[12] Landauer, W.: Rumplessness in chicken embryos produced by the injection of insulin and other chemicals. J. Exp. Zool. *98*:65–77, 1945.

[13] Duraiswami, P.: Insulin-induced skeletal abnormalities in developing chickens. Br. Med. J. *2*:384–90, 1950.

[14] Brinsmade, A. B., Bürchner, F., and Rübsaamen, H.: Missbildungen am Kaninchen embryo durch Insulininjektion beim Muttertier. Naturwissenschaften *43*:259, 1956.

[15] Horii, K., Watanabe, G., and Ingalls, T. H.: Experimental diabetes in pregnant mice: prevention of congenital malformations in offspring by insulin. Diabetes *15*:194–204, 1966.

[16] Lichtenstein, J., Guest, G., and Warkany, J.: Abnormalities in offspring of white rats given protamine zinc insulin during pregnancy. Proc. Soc. Exp. Biol. Med. *78*:398–402, 1951.

[17] Like, A., and Orci, L.: Embryogenesis of the human pancreatic islets: a light and electron microscopic study. Diabetes *21*:511–34, 1972.

[18] Steinke, J., and Driscoll, S.: The extractable insulin content of pancreas from fetuses and infants of diabetic and control mothers. Diabetes *14*:573–78, 1965.

[19] Adam, P., Teramo, K., Raiha, N., Gitlin, D., and Schwartz, R.: Human fetal insulin metabolism early in gestation. Diabetes *18*:409–15, 1969.

[20] Kalhan, S., Schwartz, R., and Adam, P.: Placental barrier to human insulin I^{125} in insulin-dependent diabetic mothers. J. Clin. Endocrinol. Metab. *40*:139–42, 1975.

[21] Nishimura, H., and Shiota, K.: Summary of comparative embryology and teratology. *In* Handbook of Teratology, Vol. 3. New York, Plenum Press, 1977, p. 119.

[22] Moore, K.: The Developing Human, 2nd edit. Philadelphia, W. B. Saunders, 1977.