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CONGENITAL MALFORMATION AND MATERNAL DIABETES MELLITUS*

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Few papers have appeared in the literature presenting a long-term follow-up of children born to diabetic mothers[1-5]. This is mainly because the survival rate of such children in the neonatal period was quite low[6-8]. Since the establishment of intensive care units, however, many high-risk babies have been able to overcome the critical neonatal period, thus enabling pediatricians to follow their progress at later stages.

It has been observed that as the follow-up period in children of diabetic mothers increases, so also does the rate of congenital anomalies[9-15]. Indeed, the authors of the present study on congenital abnormality in infants born to diabetic mothers found that the anomaly rate of the surviving children rose from 7.9% (diagnosed at birth) to 15.9% as a result of the additional anomalies discovered during follow-up.

Material and Methods

During a ten-year period at the Buffalo General Hospital at Buffalo, New York (USA), 129 children were born to 56 diabetic mothers. Of these children, 25 were stillborn, 16 died in the neonatal period and 88 survived. The entire group was analyzed for the incidence of congenital abnormality. Hospital records and autopsy findings were scrutinized in the cases of stillborn and neonatal deaths.

The Buffalo findings were supplemented by a study carried out at the Hacettepe University in Ankara, Turkey, where forty diabetic mothers and their forty-four children were examined for the incidence of congenital abnormality. Here again, autopsy reports were reviewed where appropriate.

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TABLE I

CONGENITAL ANOMALIES IN INFANTS BORN TO 56 DIABETIC MOTHERS

a. Congenital anomalies of children diagnosed at birth

Case No.*	Congenital Anomaly
6 - 1	Urethral structure
11 - 3	First degree of hypospadias
20 - 3	Absence of the left first metacarp
23 - 4	Severe pulmonary stenosis and absence of left pulmonary artery
29 - 7	Syndactyly in the foot
35 - 1	Atresia of distal colon
35 - 2	Complete situs inversus

b. Congenital anomalies of children diagnosed during follow-up

Case No.	Congenital Anomaly	Age at diagnosis
16 - 3	Mild pulmonary stenosis, ventricular septal defect (VSD)	10 years
20 - 4	Bilateral first rib anomaly	4 years
20 - 5	Transposition of the aorta, VSD, patent ductus arteriosus (PDA), hypoplasia of pancreas	7 years (exitus in surgery)
29 - 1	Tetralogy of Fallot Hearing defect	2 months (Blalock operation)
33 - 3	Congenital myopia	2 years
34 - 3	PDA, pyloric stenosis	3 months
43 - 1	VSD	6 years

c. Congenital anomalies in stillborns

Case No.	Congenital Anomaly
34 - 1	Anencephaly, cleft palate, microphthalmus, syndactyly
53 - 2	Anencephaly with partial craniospinal rachischisis
16 - 2	Transposition of the great vessels, VSD, PDA

d. Congenital anomalies in infants who died in the neonatal period

Case No.	Congenital Anomaly
4 - 1	Microcephaly
14 - 2	Duplication of ureters (Post mortem findings)
23 - 3	Bilateral harelip, cleft palate, VSD, malrotation of the intestine, hydrocephalus, agenesis of the corpus callosum
58 - 4	Congenital heart disease diagnosed clinically (no autopsy)
63 - 3	Bilateral kidney agenesia
71 - 4	Hydrocephaly

* The first number refers to the mother's study number and the second to that of the child.

The control groups of the study consisted of 22,175 and 4,400 children at Buffalo and Hacettepe Hospitals, respectively. These children were born to non-diabetic mothers at the same hospitals during the study period.

Findings

The full list of congenital anomalies observed in the 129 children forming the Buffalo group are shown in Table I. Congenital abnormality was observed in 14 of the 88 living children (15.9%), three of the twenty-five stillborns (12.0%) and six of the sixteen infants (37.5%) who died in the neonatal period, giving an overall congenital anomaly rate of 17.8%.

Congenital anomaly was found at birth in 5 of the 44 cases studied at Hacettepe University.

The congenital anomalies in the babies born to diabetic mothers at Hacettepe University are as follows:

1. Bilateral hypoplasia of femur and cleft palate
2. Cleft palate, Down's syndrome
3. Meningocele
4. Pylonoidal sinus tied to the spinal canal
5. Bilateral hydronephrosis associated with bladder neck hypertrophy

A total of 23 out of the 129 children (17.8%) born to diabetic mothers in the Buffalo study group were found to have congenital abnormalities as compared to only 1.4% in the control group. For the Hacettepe group, the incidence of congenital abnormalities was 5 out of 44 cases (11.4%) as compared to 1.2% for the control group.

The relationship of congenital anomalies to complications of diabetic pregnancy

Polyhydramnios. It is seen in Table II that when polyhydramnios complication exists in the diabetic pregnancy, congenital anomalies are more frequently observed. Of the 13 cases in Buffalo where polyhydramnios complicated the pregnancy, seven produced confirmed congenital anomaly. The resulting rate of 53.8% is statistically significant when compared to pregnancies in which polyhydramnios was not observed (Table II, $p < 0.001$).

Toxemia. 44 of our diabetic pregnancy cases were complicated by toxemia. Congenital anomaly was found in 6 of these (13.6%). In pregnancies not com-

plicated by toxemia, this rate was found to be 20.2%. Consequently, it was seen that a positive relationship does not exist between toxemia and congenital anomaly (Table II, $p > 0.001$).

Acidosis. Congenital anomaly was found in 8 of the 33 cases in which pregnancy was complicated by acidosis. Statistically it was seen that acidosis does not play a role in the formation of congenital anomaly ($p > 0.001$, Table II).

One of the 8 pregnancies in which acidosis was diagnosed ended with intrauterine death: anencephaly was found in this case. Another infant died in the neonatal period: the autopsy revealed hydrocephaly along with many other anomalies. In the remaining 6 cases complicated by acidosis, cardiovascular, gastrointestinal, urinary and skeletal anomalies were found. The infants with congenital anomaly at Hacettepe did not display any distinctions in terms of pregnancy complications.

TABLE II

THE RELATIONSHIP OF CONGENITAL ANOMALIES TO COMPLICATIONS OF PREGNANCY

Complication of pregnancy		Total	Number of cases of congenital anomaly	%
Polyhydramnios	Yes	13	7	53.8
$p < 0.001$	No	115	16	13.9
Toxemia	Yes	44	6	13.6
$p > 0.001$	No	84	17	20.2
Acidosis	Yes	33	8	24.2
$p > 0.001$	No	95	15	15.8

The relationship of congenital anomalies to the severity of diabetes

Congenital anomaly was found to reach 20.4% in the infants of mothers in group C of White's[8] classification and 66.7% in those whose mothers were in the F group. Although the incidence of congenital anomaly tended to increase in cases of advanced maternal diabetes such as groups C and F, the White's classification groups were too small for there to be a statistical correlation between the severity of diabetes and congenital anomaly (Table III).

TABLE III

THE EFFECT OF THE SEVERITY OF DIABETES ON CONGENITAL ANOMALY

White's Diabetic Classification	Total	Number of cases of congenital anomaly	%
Group A	9	0	0
Group B	42	8	19.0
Group C	49	10	20.4
Group D	26	3	11.5
Group E	0	0	0
Group F	3	2	66.7
Diabetic group (total)	129	23	17.8

The effect of insulin and other medicines on congenital anomaly

Mothers used insulin in 117 of the 129 Buffalo pregnancies. Since skeletal anomaly was found in only 3 cases, it is clear that insulin alone is not responsible for skeletal anomalies observed in children of diabetic mothers.

None of the mothers in the Hacettepe group was on insulin.

Discussion

A number of important factors contribute to discrepancies in the reported rates of congenital anomalies in children born to diabetic mothers[1-5,7,11,13]. These include the description of congenital anomalies, the methods used in their diagnosis, and the follow-up period for these children.

1. Description of congenital anomalies

While certain authors have covered only major congenital anomalies in their reports, others have included minor findings as well. In their research on the Turkish population, for instance, Say et al[16] found a clear difference in the occurrence of anomalies after they were classified as major and minor (Table V). To avoid ambiguity, a complete list of the congenital anomalies encountered in the present study was given in Table I.

2. Methods used in the diagnosis of congenital anomalies

Under this heading it is essential to specify whether the diagnosis was made by examination only, whether the same doctor administered all the check-ups, whether

x-rays were used, whether the child is alive or dead, and most important, whether an autopsy was performed in the event of death. All these factors may affect the rate of diagnosed congenital anomalies.

It has been found that in studies where the number of autopsies is high, the congenital anomaly ratio is also high[7]. This has given rise to the argument that the high number of autopsies conducted on infants born to diabetic mothers might increase the congenital anomaly ratio. For example, the Driscoll et al[7] series of 95 cases, each of them involving post mortem examinations, produced the high anomaly rate of 24.2% (Table IV).

This objection can not be sustained for our study. Although the autopsy rate for the children born to diabetic mothers was as high as 64% for stillborns and 81.3% for those who died in the neonatal period, the same autopsy rate was observed for infants born to non-diabetic mothers in the same hospital during the same period. The rate of congenital anomaly for this latter group, which could be called the control group, was found to be 1.4%. The anomaly rate for the children born to diabetic mothers, on the other hand, was 17.8%, or 12.7 times the normal rate. In

TABLE IV

INCIDENCE OF CONGENITAL ANOMALY IN CHILDREN OF DIABETIC MOTHERS

Author	Number of children of diabetic mothers	Congenital anomaly %
White and Hunt[8]	125	16
Pedersen et al[11]	853	6.4
Gellis and Hsia[3]	711	1.6
Hagbard et al[4]	350	7.6
Hiekkala and Koskenoja[5]	165	2.6
Tiisala et al[12]	123	9.8
Farquhar[2]	93	17.4
Breidahl[1]	200	20
Connor[13]	206	16.8
Driscoll et al[7]	95	24.2
Day and Insley[14]	205	12
Present study (Buffalo)	129	17.8
Present study (Hacettepe)	44	11.4

the Hacettepe group, congenital anomaly at birth for the offspring of diabetic mothers was found to be 11.4%, compared to only 1.2% in the control group (Tables IV and V).

TABLE V

INCIDENCE OF CONGENITAL ANOMALY IN NORMAL POPULATIONS

Author	Total number of children	Congenital anomaly %
Pedersen et al[11] (non diabetic mothers)	121	2.1
McIntosh et al[9] (follow up until 1 year old)	5,964	7.5
Hendricks[34]	210,947	0.74
Say et al[16] (in liveborn infants)	9,947	Minor 6.27 Major 2.0
Day and Insley[14]	205	6
Present study (Control group, Buffalo)	22,175	1.4
Present study (Control group, Hacettepe)	4,400	1.2

3. Follow-up period

As the follow-up period for the children of diabetic mothers increased, so did the rate of congenital anomalies[9]. In the Buffalo study, seven congenital anomalies were found during follow-up, which when added to the seven diagnosed at birth increased the overall rate to 17.8%.

In five of the seven cases diagnosed later, major anomalies such as congenital heart defects were found. This shows that it is not always possible to diagnose even major anomalies at birth.

The importance of the time factor in establishing the rate of congenital anomaly is not limited to the children of diabetic mothers. McIntosh et al[9], for example, found a 3.24% rate of congenital anomaly in normal populations at birth, which rose to 7.5% after a one-year follow-up period (Table V).

As already noted, the congenital anomaly rates for children born to diabetic mothers vary significantly as reported by different authors. In view of this, we have

felt it appropriate to present, by way of comparison, other reported rates in conjunction with our own findings (Tables IV and V).

As can be seen clearly from Tables IV and V, the occurrence of congenital anomaly is much less frequent in normal population groups than in the children of diabetic mothers.

The relationship of congenital anomalies to pregnancy complications

Polyhydramnios is frequently encountered in pregnancies which result in congenital anomalies. Stevenson[17] found a congenital anomaly rate of 23.5% when polyhydramnios complicated diabetic or nondiabetic pregnancies. Dekaban and Baird[18] found polyhydramnios in seven of 110 pregnancies. Of these seven, two infants survived, three died in utero and one died in the neonatal period. One of those who survived is reportedly neurologically abnormal.

Polyhydramnios complicated pregnancy in 13 of our cases. Congenital anomalies in these children were statistically significant, reaching 53.8% (Table II).

Acidosis. It was postulated that cerebral metabolism of the developing fetus may be affected by a high concentration of ketone bodies during pregnancy. In this period, different structures in brain development have a faster metabolism and so are more vulnerable[19]. Taylor[20] believes that congenital anomaly is related to the inadequate control of diabetes, since the disease can promote hyperglycemia and acetonuria after conception.

Thirty-three of our cases involved pregnancy complicated by acidosis. Of these, eight were found to have congenital anomalies. This result was not significant statistically ($p > .001$, Table II).

Toxemia. Many reports exist in the literature on the relationship between pregnancies with toxemia and fetal losses[21]. A wide variation, ranging from 8% to 48%, exists in the reported rates of fetal loss in diabetic pregnancies[22]. Toxemia is seen mainly in diabetic pregnancies with long-term renal complications. Hagbard[23] agrees with this opinion by finding toxemia frequent in those with long-term diabetes. None of these authors has studied the relationship between toxemia and congenital anomaly.

Toxemia complicated diabetic pregnancy in 44 of our cases. Congenital anomaly was found in six of these. In fact, it is evident that toxemia can not be the cause of congenital anomaly since it often appears in the last trimester of pregnancy when organogenesis has already been completed.

The relationship of congenital anomaly to the severity of diabetes

Studies carried out by White[24], Pedersen et al[11], and Connor[13] have shown that congenital anomalies increase in proportion to the severity of diabetes. Breidal's study[1] and that of Tiisala et al[12] did not establish such a correlation. The findings of our study, as seen in Table III, show the anomaly rate to be highest (66.7%) in Group F of White's classification, constituting the severest diabetic cases complicated by vascular disorders. However, these results and similar findings in the literature must await clarification in future studies which use larger numbers of cases.

The effect of insulin and other medicines on congenital anomaly

Insulin. Duraiswami[25] showed that skeletal anomalies may develop if insulin is injected into chicken eggs during the first 48 hours of incubation. Hence, a relationship between insulin given to diabetic mothers and congenital anomaly was considered. Reis et al[26] found fewer congenital anomalies in cases where the mother did not need insulin during the first months of pregnancy. Pedowitz and Shlevin[22] called attention to the potential danger of insulin. However, in fifty cases of congenital anomaly in the Pedersen et al[11] series, only eight mothers had insulin comas. Moreover, there was no occurrence of congenital anomaly in Hagbard's thirty cases of mothers who developed insulin coma during pregnancy[23]. These findings would tend to show that insulin does not play a role in the formation of congenital anomaly in humans.

Skeletal anomalies in infants born to diabetic mothers have been reported in the literature, including sacral agenesis[27], the absence of the second, third and fourth fingers, and the absence of a third of a foot[18].

Four of our cases involved skeletal anomalies. One of these was a focomelia case, where the child was born before the onset of clinical diabetes. Another two concerned siblings. The first metacarp of the hand was missing in one, and bilateral rib anomaly was found in the other. Acidosis and coma were observed in the pregnancy of the rib anomaly case. It was learned that the mother had used insulin in both of these pregnancies. The other instance of skeletal anomaly was in a baby who died in utero. Partial craniospinal split together with anencephaly was found at autopsy.

Other medicines. Larsson and Sterky[28] reported malformation in the child of a diabetic mother who had used tolbutamide during pregnancy and indicated that this medicine should be used very cautiously during pregnancy. Another study[29] found the tolbutamide level higher in the cord blood than in the mother's blood, indicating that the drug enters the placenta. DeMeyer's study[30] compared the teratogenic effects on rats of tolbutamide, chlorpropamide (Diabenese) and carbutamide and

found malformation in rates of 41%, 37% and 90%, respectively. Eudean and Smith[31] reported tolbutamide usage in three pregnancies of two mothers and found that all three children were normal.

None of the Buffalo mothers used oral antidiabetics. Two mothers at Hacettepe took Diabenese during their pregnancies, but their children showed no congenital anomaly.

Since diabetes is known to be a hereditary disease, one may ask about the rate of congenital anomaly in children of diabetic fathers.

Koller[32] studied 123 children of 55 diabetic fathers and found congenital dislocation of the hip in 2 children. Rubin[33] studied congenital anomaly in the children of 168 diabetic and an equal number of nondiabetic fathers. Out of 463 pregnancies, 3 children had congenital anomalies. The rate for the children of diabetic fathers was 0.65%, which is not statistically different from the rate in the control group of 0.29%.

Pedersen et al[11] established a congenital anomaly rate of 2.1% in their research on 121 children born to non-diabetic mothers. The rate found by Say et al[16] for normal Turkish society was 8.27%. Since the diabetes factor was not known in Say's research, diabetes may have contributed to the wide difference in the results of the two researchers.

As all of these discussions show, it is not yet clear why congenital anomaly is frequently observed in the children of diabetic mothers, an observation likewise made in a recent publication[35].

De Meyer[15] suggested that possible genetic factors should be investigated to shed light on the relation of maternal diabetes and congenital anomalies in their children.

In conclusion, we can say that whatever the cause, the frequency of congenital anomaly is definitely higher in children born to diabetic mothers than in children of normal mothers.

Summary

One hundred twenty-nine children born to 56 diabetic mothers in Buffalo Children's Hospital (New York, U.S.A.) were analyzed for the incidence of congenital abnormality. Three of the 25 stillborns (12%), six of the sixteen babies who died during the neonatal period (37.5%) and 7 of the 88 children who survived the neonatal period (7.95%) had congenital abnormalities.

An additional 7 cases of congenital abnormality were found during the follow-up, increasing the incidence of anomaly in surviving children born to diabetic mothers from 7.9% to 15.9%.

In total, in the Buffalo group 23 of the 129 (17.8%) children born to diabetic mothers were found to have congenital abnormalities as compared to only 1.4% in the control group.

The incidence of congenital abnormalities at birth was found to be 5 out of 44 cases (11.4%) in a group of babies born to diabetic mothers at Hacettepe University Hospital (Ankara) as compared to 1.2% for the control group.

The relationship between congenital anomalies and complications of pregnancy, severity of diabetes and effects of insulin and other medicine on congenital anomalies were discussed.

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