Special Article

Infants of Diabetic Mothers

Neonatal Problems and Their Management

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SUMMARY

A study of neonatal problems of 329 liveborn infants of diabetic mothers indicates that prematurity is the single most significant factor influencing outcome. The direct relationship of prematurity to increased incidence of respiratory distress syndrome, hyperbilirubinemia, and neonatal mortality is demonstrated. Severity of maternal diabetes, while extremely important in relation to stillbirth, does not seem to be as significant a factor in liveborn infants. The present plan of care designed to deal with these problems in liveborn infants at the Boston Lying-in Hospital has been presented. DIABETES *14*:157-61, March 1965.

Pregnancy in the diabetic woman has become a more frequent occurrence in recent years.[1-3] The more successful management of childhood diabetes, the greater willingness of severe diabetics to undertake pregnancy, and the increased number of physicians prepared to manage pregnant diabetics have all contributed to this trend. Indeed, the successful management of so many diabetic pregnancies has resulted in an increase in neonatal problems for the pediatrician. It was felt that a description of some of these neonatal problems in a relatively large series of patients might prove worthwhile. Material for this paper is based on experience in the pediatric management of 329 *liveborn* infants of the Joslin Clinic group delivered at the Boston Lying-in Hospital between Jan. 1, 1959 and Dec. 31, 1962. Infants were observed in the delivery room at birth and subsequently managed by one or the other of the authors. The infants will be discussed in terms of severity of maternal diabetes, obstetrical characteristics, condition immediately following delivery, the respiratory distress syndrome, hyperbilirubinemia, and infant mortality. A description of their clinical management at the Boston Lying-in Hospital will follow.

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Maternal characteristics

Table 1 indicates severity of maternal diabetes by the White classification.[4] Classes A, B, and C represent diabetes of relatively short duration without vascular complications while D and F patients have had diabetes for twenty years or more with evidence of vascular disease. Class E, calcification of pelvic blood vessels, is omitted since routine pelvic X rays are no longer taken. It is evident that slightly more than half of the infants in the present series belong to the more severe classifications of diabetes. Table 2 shows approximately one third of the total group of mothers were primiparas and two thirds were delivered by cesarean section. About two thirds of the liveborn infants were delivered at thirty-six to thirty-seven weeks gestation, considered to be optimum time for delivery of the mother with diabetes, while nearly one third were delivered earlier.* The ma-

TABLE 1

Severity of maternal diabetes; White Classification (329 liveborn infants)

Class	Number	Per cent
A	11	3
B	61	19
C	73	22
D	163	50
F	21	6

TABLE 2

Obstetrical characteristics (329 liveborn infants)

	Number	Per cent
Parity:		
primiparas	100	30
multiparas	229	70
Method of delivery:		
cesarean section	229	70
pelvic delivery	100	30
Gestational age:		
less than 36 weeks	95	29
36-37 weeks	214	65
Over 37 weeks	20	6

*Gestational age has been used as an indicator of prematurity throughout this paper, since the tendency of infants of diabetic mothers toward higher birth weights at all gestational ages gives a false impression of physiologic maturity.

jority of the infants delivered earlier than thirty-six weeks were delivered for obstetrical indications such as severe maternal diabetes, irregular fetal heart, or decrease in fetal activity. They represent a substantial group of infants even more premature than the rest.

Respiratory distress syndrome

Once an infant is delivered alive, the greatest threat to his subsequent course becomes the "idiopathic respiratory distress syndrome of the newborn."[5] This clinical condition is characterized by rapid respiratory rate, costal retractions, generalized cyanosis and labored breathing. X ray of the lungs shows a diffuse increase in density with a reticulo-granular appearance throughout.[6] If the infant dies, the most likely autopsy finding is resorption atelectasis with hyaline membrane formation.[7] However, bronchopneumonia, pulmonary hemorrhage, or even congenital anomalies of the heart or lungs may give the same clinical picture during life. For this reason if the patient recovers, one is never absolutely certain of the anatomical diagnosis—hence the use of the term "idiopathic respiratory distress syndrome." This respiratory distress syndrome (RDS) was present in ninety of the 329 liveborn infants (27 per cent). The remainder had no evidence of respiratory distress severe enough to require oxygen therapy. It was found in this series that the incidence of respiratory distress was the same for both pelvic and cesarean delivery.

Table 3 lists three different criteria for respiratory difficulty immediately following delivery: low Apgar scores[8] at one and five minutes and need for oxygen therapy to relieve cyanosis in the delivery room. The figures indicate that approximately one half of infants with these abnormalities at delivery went on to develop respiratory distress. By contrast only one in five infants without these findings in the delivery room later showed respiratory distress. These data support the view that the pathophysiology of the respiratory distress syndrome starts very shortly after birth, or even prior to delivery.

TABLE 3

RDS* related to clinical state at delivery (329 liveborn infants)

	Total number	Number with subsequent RDS	Per cent
One minute Apgar 6 or less	56	29	52
One minute Apgar over 6	273	61	22
Five minute Apgar 6 or less	32	16	50
Five minute Apgar over 6	297	74	25
Needed O_2 in delivery room	75	41	55
No O_2 in delivery room	254	49	19

*Respiratory distress syndrome

Table 4 shows the relation of respiratory distress to gestational age at delivery. Incidence falls progressively from a high of 88 per cent of infants delivered before thirty-two weeks down to a low of 15 per cent for infants born after thirty-seven weeks gestation. Degree of prematurity at birth appears to be quite directly related to the development of respiratory distress, as is true for nondiabetic mothers' premature infants. However, approximately one half of the ninety infants with respiratory distress came from the two thirds of the total group delivered at thirty-six to thirty-seven weeks. Thus, although prematurity increases the likelihood of this syndrome, a still significant number of infants delivered at the optimal thirty-six to thirty-seven weeks went on to develop respiratory distress.

TABLE 4

RDS* related to gestational age (329 liveborn infants)

Gestational age (wks.)	Total number	Number with RDS	Per cent with RDS
Under 32	8	7	88
32-33	16	9	56
34-35	71	29	41
36-37	214	42	20
Over 37	20	3	15
Total	329	90	

*Respiratory distress syndrome

There is a less linear relationship between severity of maternal diabetes and the development of respiratory difficulties (table 5). Infants of class A mothers rarely develop RDS, while those of class F mothers show a 50 per cent incidence of distress severe enough to require oxygen therapy. Infants from classes B, C, and D are subject to nearly identical risks of respiratory distress; this emphasizes the need for careful management of even the mild or short-term pregnant diabetic, while being prepared for higher morbidity in the long-term diabetic with renal disease.

Hyperbilirubinemia

Hyperbilirubinemia (defined as a serum bilirubin level above 15 mg. per 100 ml.) in the newborn infant may be related to various circumstances such as blood group incompatibility, prematurity, and infection. The incidence in a large group of full-term infants free of infection and of hemolytic disease is less than 2 per cent,[9] but prematurity alone may result in an incidence of hyperbilirubinemia up to 30 per cent.[10] It has been recognized that there is an increased incidence of hyper-

TABLE 5

RDS* related to class of diabetes (329 liveborn infants)

Class	Total number	Number with RDS	Per cent with RDS
A	11	1	9
B	61	15	25
C	73	20	27
D	163	43	26
F	21	11	52

*Respiratory Distress Syndrome

bilirubinemia in infants of diabetic mothers, presumed to be related to immature liver function.[9] Approximately 40 per cent of the 329 infants in this series had serum bilirubin levels over 15 mg. per 100 ml. Table 6 shows that a relationship does exist between gestational age and incidence of hyperbilirubinemia; the apparent low incidence in the smallest babies is due in part to high mortality prior to the onset of icterus. Nearly 60 per cent of those infants surviving respiratory distress syndrome had hyperbilirubinemia. However, this again may be a function of prematurity, rather than respiratory distress.

TABLE 6

Gestational age related to hyperbilirubinemia (329 liveborn infants)

Gestational age (wks.)	Total number babies	Number with bilirubin over 15 mg. per cent	Per cent
Under 32	8	2	25
32-33	16	9	56
34-35	71	37	53
36-37	214	82	38
Over 37	20	3	15
Total	329	133	40

Mortality

During the period 1959 to 1962, full-term neonatal mortality at the Boston Lying-in Hospital varied between 0.3 and 0.5 per cent while premature mortality (under 2,500 gm. birth weight) was 9.0 to 13.0 per cent resulting in an over-all neonatal mortality rate of 1.5 per cent. Thirty of the 329 liveborn infants in this series died during the newborn period, a neonatal mortality rate of 9.0 per cent.* Autopsy was performed on twenty-nine of these infants and a principal cause of death could be found in all but one. The one infant not autopsied weighed 650 gm., was extremely immature clinically, and lived only a little over one hour. Table 7 shows that almost one half of the infants had hyaline membranes and resorption atelectasis as the primary cause of death. The remainder were divided among infection, congenital malformations and pulmonary hemorrhage. Thus the great majority presented symptoms of respiratory distress during life. Among the infants who died, hyaline membrane disease was found frequently at all gestational ages. However, pulmonary hemorrhage was found only in the more premature infants. The increased over-all mortality at lower gestational ages is apparent; in fact two thirds of the total deaths occurred in the group of ninety-five infants delivered at less than thirty-six weeks gestation.

Table 8 re-affirms the low risk of mortality for infants born of class A mothers. However, the risk of death from hyaline membrane formation or from congenital malformations is very much the same for all infants from mothers classified B through F. The increased mortality of class F babies may be because 75 per cent of these were delivered prior to thirty-six weeks gestation. Prematurity becomes a more significant factor in this group of infants leading to both a higher incidence of clinical respiratory distress and a higher mortality. The harmful effect of prematurity appears to be demonstrated in all the data presented.

Plan of Care

Pediatric management begins in the delivery room, where one of the "team" pediatricians is in attendance. Resuscitative measures and immediate evaluation are carried out by him as soon as delivery is accomplished. The practice is to keep the infant's head down, apply bulb suction to nose, mouth and pharynx, and then at one minute of age evaluate the initial Apgar scoring. Quick over-all inspection, further suctioning and the two-minute Apgar scoring usually show a baby in good condition, pink and breathing well. If this is not the case, more elaborate resuscitative measures such as suction under direct vision, intubation and positive pressure oxygen may be required. In the past, gastric suction was usually carried out at about this time. At present, this is believed to be unnecessary so early, as it may lead to reflex laryngospasm and secondary apnea. Gastric suction may be done later for any baby with excessive secretions.

If the infant behaves well, the time between two and five minutes is used to tie the umbilical cord and make a slightly more extensive inspection followed by the five minute Apgar scoring. If there is no obvious distress, and if there are no apparent major malformations, the infant may then be left to the nursing staff for wrap-

*This paper considers only liveborn infants of diabetic mothers. However, during the four-year period under study the stillbirth rate in diabetic pregnancies was approximately 6 per cent compared to 1.5 per cent in the nondiabetic population.

TABLE 7

Principal causes of death related to gestational age (329 liveborn infants)

Gestational age (wks.)	Total number	Total deaths	Per cent	Hyaline membrane disease	Infection	Congenital anomaly	Pulmonary hemorrhage
Under 32	8	6	75	4	0	0	1
32-33	16	5	31	0	2	1	2
34-35	71	9	13	5	1	3	0
36-37	214	10	5	4	3	2	0
Over 37	20	0	0	0	0	0	0
Total	329	30	9	13	6	6	3

TABLE 8

Principal causes of death related to severity of diabetes (329 liveborn infants)

Class of diabetes	Total number	Total deaths	Per cent	Hyaline membrane disease	Infection	Congenital anomaly	Pulmonary hemorrhage
A	11	0	0	0	0	0	0
B	61	7	11	3	1	2	0
C	73	4	5	2	1	1	0
D	163	15	9	7	3	3	1
F	21	4	19	1	1	0	2

ping-up to keep warm, eye prophylaxis, administration of a small dose of Vitamin K and transfer to the premature nursery. As soon as the infant's condition has stabilized following admission, a complete physical examination is carried out, supplemented as soon as feasible with a chest X ray—this not only to detect possible early changes of respiratory distress (RDS), but also as a screening for possible malformations.

All infants are kept in incubators for forty-eight to seventy-two hours to facilitate observation as well as to preserve a stable temperature with high relative humidity. The nursing staff observes and records respiratory rate and character, pulse, color, and activity every one to two hours, for the first forty-eight hours of life; longer for sick infants. Removal of secretions is carried out when necessary, the position of the infant is changed every one or two hours, but otherwise handling is kept at a minimum. For infants with no distress, oral 10 per cent glucose solution is started at twenty-four hours and milk formula at forty-eight hours.[10]

Infants with respiratory distress syndrome are frequently found to be in difficulties within the first hour of life, and are almost always easily identifiable by three or four hours of age, on the basis of clinical signs and symptoms, need for oxygen, and X ray changes in the lungs. A small group of infants with early signs of distress prove to have only transient difficulties, and may be without distress by four to six hours of age. These infants usually have normal X rays and do not show progressively falling oxygen tension in their arterial blood. All infants with increasing respiratory distress are placed in Isolette incubators, where sufficient oxygen is provided to prevent cyanosis, if possible. In the very sick infants, this may require close to 100 per cent oxygen, provided by a mask held directly over the face. Mechanical devices to provide oxygen under increased pressure have been employed from time to time, with inconclusive results. It has been found helpful to sample umbilical arterial blood at frequent intervals in order to follow oxygen tension, carbon dioxide tension, *p*H, and hematocrit. Supportive therapy, in the form of intravenous glucose solution containing $NaHCO_3$, can be provided as needed to help combat acidosis. Whole blood may also be given for a falling hematocrit. When signs of congestive heart failure are present, rapid digitalization has been used. However, this therapy has not seemed to be helpful in cases where hyaline membrane disease is thought to be the underlying pathology. Antibiotics are given because of the possibility of secondary infection, and because of the difficulty of distinguishing pneumonia from other causes of neonatal respiratory distress.

Infants who survive the respiratory distress syndrome are usually improving clinically and radiologically by the third or fourth day, when they can start on oral feedings and may remain free of cyanosis in decreasing concentrations of oxygen. After the fifth or sixth day, they are out of oxygen, off antibiotics and feeding by bottle. These babies are more premature than their weights would indicate and frequently are not ready for home care as soon as other babies of comparable weight.

As mentioned previously, elevation of serum bilirubin, not related to blood group incompatibility, is a frequent complication in infants of diabetic mothers. Icteric infants are observed carefully both clinically and by the laboratory. Indications for exchange transfusion depend on the infant's size, age, on the state of the central nervous system, as well as on the level of serum bilirubin. The level of 20 mg. per cent of indirect bilirubin is used as an approximate guide for exchange transfusion, with exceptions in both directions.

In addition to the problems of respiratory distress and hyperbilirubinemia, infants of diabetic mothers suffer an increased incidence of congenital malformations. These are searched for by continuous clinical observations, by chest X ray, and by histologic examination of placenta and umbilical cord. It is inevitable, however, that some will be missed, to turn up in later months or years. It is hoped that the current follow-up program, aided by a grant from the National Institute of Neurological Diseases and Blindness, will help to elucidate the true incidence of congenital malformations, as well as determine the neurologic outcome of these babies who undergo such varied stress in the neonatal period.

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REFERENCES

1 Gellis, S., and Hsia, D. Y.: The infant of the diabetic mother. Amer. J. Dis. Child. 97:1-41, 1959.

2 Farquhar, J. W.: The child of the diabetic woman. Arch. Dis. Child. 34:76-96, 1959.

3 Pedersen, J., and Brandstrup, E.: Fetal mortality in pregnant diabetics. Lancet 1:606, 1956.

4 White, P., Gillespie, L., and Sexton, L.: Use of female sex hormone therapy in pregnant diabetic patients. Amer. J. Obstet. Gynec. 71:57-69, 1956.

5 Rudolph, A. J., and Smith, C. A.: Idiopathic respiratory distress syndrome of the newborn. J. Pediat. 57:905-21, 1960.

6 Peterson, J. G., Jr., and Pendleton, M. E.: Contrasting roentgenographic pulmonary patterns of hyaline membrane and fetal aspiration syndromes. Amer. J. Roentgen. 74:800-13, 1955.

7 Driscoll, S. G., Benirschke, K., and Curtis, G. W.: Neonatal deaths among infants of diabetic mothers. Amer. J. Dis. Child. 100:818-35, 1960.

8 Apgar, V., Holaday, D. A., James, L. S., Weisbrot, I. M., and Berrien, C.: Evaluation of the newborn infant: Second Report. JAMA 168:1985, 1957.

9 Olsen, B. R., Osler, M., and Pedersen, J.: Neonatal jaundice in infants born to diabetic mothers. Danish Med. Bull. 10:18-20, 1963.

10 Lucey, J. F.: Hyperbilirubinemia of prematurity. Pediatrics 25:690-710, 1960.

11 Hubbell, J. P., Drorbaugh, J. E., Rudolph, A. J., Auld, P. A. M., Cherry, R. B., and Smith, C. A.: "Early" versus "late" feeding of infants of diabetic mothers. New Eng. J. Med. 265:835-37, 1961.