ENHANCEMENT OF FETAL SURVIVAL IN PREGNANCY WITH DIABETES

ALBERT C. LAMMERT, M.D.,
Department of Obstetrics and Gynecology
WILLIAM M. MICHENER, M.D., M.S.(Pediat.),
Department of Pediatrics
and
O. PETER SCHUMACHER, M.D., PH.D.
Department of Endocrinology and Metabolism

EFFORTS to reduce maternal mortality and morbidity in the pregnant woman with diabetes mellitus have been rewarded with gratifying results throughout the world, yet the associated fetal mortality has not been correspondingly reduced. With close observation and early vigorous treatment, maternal complications such as acidosis and preeclampsia are either preventable or less threatening than formerly, with the result that maternal mortality among women with diabetes has been reduced from 50 percent in the days before insulin, to nearly zero.[1] Although the rate of fetal survival has improved during this time, mortality rates of from 10 to 50 percent are still reported.[1] During a three-year period (July 1, 1959, through June 30, 1962) the fetal mortality among 390 diabetics in the Cleveland area was 21.5 percent.[2] During this same period, 19 babies were born to 14 diabetic mothers at the Cleveland Clinic Hospital, with one fetal death, or a fetal mortality rate of 5.2 percent.

The purpose of this report is to present the principles of management of diabetes and pregnancy, and of the newborn, which have been carried out in this group of 14 diabetic patients and their infants at the Cleveland Clinic. The cooperative efforts of three specialties are involved—obstetrics, endocrinology and metabolism, and pediatrics—and we are encouraged by the favorable results.

Obstetric Management

Among diabetic pregnant women, the incidence of preeclampsia, stillbirth, and other complications of pregnancy is high; therefore, a careful history of prior pregnancies is taken at the time of the initial examination of the pregnant diabetic. The birth weight of previous children is noted especially, because it is well known that the babies frequently are large. An appraisal of the overall situation is made, and the general plan of management is outlined to the patient. The added hazards of pregnancy are presented to the patient in such a manner that she will be alerted but not alarmed. She is examined at monthly intervals, with strict attention to weight gain, blood pressure, size of uterus, presence or absence of albuminuria, and, when appropriate, the presence of fetal heart tones. The management of the diabetes mellitus is in the hands of the internist.

During the last trimester, when the incidence of preeclampsia rises sharply, the patient is seen every other week, and every week if there is a sign of impending complication. Fluid retention and sudden weight gain may be an early warning sign. Should this occur and be accompanied by hypertension and/or albuminuria, hospitalization is indicated. The size and presentation of the fetus is watched carefully, for these will influence the important decision of when and by what means the fetus will be delivered. We believe, as do others,[3, 4] that delivery from three to five weeks early offers the best chance of infant survival. Delivery before the thirty-fifth week adds the significantly great risk of prematurity, and the chance of fetal death in utero rises sharply after the thirty-seventh completed week. Selection of a date between the thirty-fifth and thirty-seventh weeks is largely a matter of clinical judgment. In general, the difficult-to-control diabetic, or the patient with a clinically gigantic fetus is delivered earlier, and the well-controlled diabetic or the patient with a clinically normal-sized fetus is delivered closer to the end of the arbitrary 35 to 37 week delivery period. In the case of severe preeclampsia or diabetes that is extremely difficult to control, elective delivery is carried out before the thirty-fifth week.

Early elective delivery is most often accomplished by cesarean section. However, with a vertex presentation, the head engaged, and the cervix soft, effaced, and partially dilated, and no evidence of disproportion present, consideration is given to induction of labor. Whatever the route of delivery, sedation is kept at a minimum, and regional anesthesia is used in order to minimize the effects on the premature infant in whom respiratory depression would materially increase the risk.

As stated, there were 19 babies delivered at the Cleveland Clinic Hospital during the period of study (*Table 1*). The ages of the 14 mothers ranged from 18 to 44 years. The known duration of the diabetes ranged from 2 to 36 years. Ten of the 14 patients were in classes C and D of White's[5] classification. Eleven of the deliveries were by elective cesarean section. Of the eight cases of vaginal delivery, spontaneous labor occurred in four, and four followed electively induced labor. Of the four spontaneous labors, three occurred before the thirty-fifth week. All four inductions were in patients who had prior vaginal deliveries. Three of these patients were three of the four who were permitted to complete 37 weeks of pregnancy. The fact that their infants each weighed no more than between six and seven pounds, points up the benefits of individualization in selection of time and method of delivery.

The incidence of preeclampsia was not so high as the 20 to 30 percent generally reported;[6] there were only two cases or 10.5 percent in 19 pregnancies.

Medical Management

The medical management of the diabetic patient during her pregnancy requires continuous cooperation among the patient, obstetrician, pediatrician, and

Table 1.—*Clinical data of 14 pregnant diabetic patients and their infants*

Mother	Age, yr.	Duration of diabetes, yr.	Diabetes mellitus, White's[5] classification	Delivery, week of pregnancy	Comment	Type of delivery	Infant		
							Birth weight, gm.	Appearance	Course
1	36	14	D	33	Preeclampsia; spontaneously ruptured membranes	Cesarean section	1,847	Normal	Hyperbilirubinemia
2	36	13	C	36	—	Cesarean section	4,111	"Typical"	No distress
3	32	5	A	36	Medical induction	Vaginal	2,863	Normal	No distress
4 (1)	23	9	C	37	—	Cesarean section	3,203	Normal	No distress
(2)	24	10	C	35	—	Cesarean section	3,300	"Typical"	Respiratory distress
5	35	13	C	36	Spontaneous labor	Vaginal	3,629	"Typical"	Respiratory distress; hyperbilirubinemia
6	19	14	D	36	—	Cesarean section	2,863	"Typical"	No distress; hyperbilirubinemia
7	38	21	D	31	Spontaneous labor	Vaginal	1,758	Normal	No distress; respiratory distress
8 (1)	18	13	D	25	Intrauterine death	Vaginal	—	—	—
(2)	19	14	D	34	3 antepartum admissions for control of diabetes	Cesarean section	3,544	"Typical"	Lethargy
9 (1)	24	9	C	34	Spontaneous labor	Vaginal	3,118	"Typical"	Convulsion; apnea; hyperbilirubinemia
(2)	26	11	C	37	Medical induction	Vaginal	2,977	Normal	Hyperbilirubinemia
10 (1)	30	10	C	36	Preeclampsia	Cesarean section	4,224	"Typical"	Apnea
(2)	31	11	C	35	—	Cesarean section	3,289	"Typical"	No distress
11	28	5	B	35	—	Cesarean section	3,544	"Typical"	Respiratory distress; Rh incompatibility (2 exchange blood transfusions)
12 (1)	41	2	A	37	Medical induction	Vaginal	2,750	Normal	No distress
(2)	44	5	A	37	Medical induction	Vaginal	3,100	Normal	No distress
13	37	36	D	35	Cesarean hysterectomy	Cesarean section	3,232	"Typical"	No distress
14	30	3	A	35	—	Cesarean section	3,856	Normal	Hyperbilirubinemia

internist for the best possible results. We are fortunate that our patients are keenly interested in the course of the pregnancy, and cooperate with us to the fullest extent. We have had two patients in whom diabetic keto-acidosis developed, even though they were being followed closely. Each patient had been testing the urine with Testape, which may have been outdated, and it was reportedly negative for sugar. In one of these instances, fetal death occurred because keto-acidosis was allowed to progress (plasma pH 6.9) as a result of the patient and her husband's lack of understanding of the symptoms, and their reliance on the negative urine test.

After an initial complete medical evaluation, including a funduscopic examination, and renal function studies by a urea clearance test, an Addis test, and a urine culture, the internist sees the patient periodically as often as once a week or more with the obstetrician. Our practice is to have the patient come in to the outpatient department before breakfast, and have her receive two meals during her day here. She is examined by the obstetrician during the course of the morning and by the internist around lunchtime, when the results are available both of the routine urinalysis and of the blood sugar determinations (fasting, and 2 to 3 hours postprandially). We may at times determine the blood sugar before breakfast, before lunch, before supper, and at bedtime when the clinical situation seems to require it. Most of our patients are on a mixture of short- and long-acting insulin, which we believe provides greater flexibility than a single type of insulin during the changing phases of pregnancy. Examples of the changing insulin requirements, and other clinical data, are summarized in *Table 2*. We have noted that the insulin requirement may rise rapidly at five months.

Each outpatient examination is coordinated with a lecture in our school for diabetic patients where each day of the week a different topic is discussed in order better to educate all of our diabetic patients. This educational process together with the patient's interest and cooperation facilitates our total program of diabetic management, particularly for the pregnant woman.

Patients are instructed to test the urine for glucose from two to four times daily, and to keep a record of the results. As was previously mentioned, we prefer reagent tablets* to reagent strips† because the strips may become outdated and are not so quantitative as the tablets in the measurement of urine glucose. Small doses of regular insulin may be needed for glycosuria as often as three times daily. Patients are also taught to test the urine for acetone.‡

During the period of hospitalization at the time of delivery our usual practice is to reduce by half the dose of long-acting insulin, giving this dose in the morning each day. If, then, the patient is unable to have oral feedings, we put regular insulin into the intravenous infusions that contain dextrose, usually adjusting the amount

Clinitest, Ames Co., Inc.
†*Clinistix, Ames Co., Inc.; Testape, Eli Lilly and Company.*
‡*Acetest powder or tablets, Ames Co., Inc.*

of insulin per unit of intravenous medication to the insulin requirement for the available glucose in her diet.

It must be emphasized that we make frequent blood-sugar determinations, as previously mentioned, during the outpatient examinations and also during the period of hospitalization. Usually we make tests twice daily, and often four times daily, even when there is no keto-acidosis present. We try to maintain the blood sugar concentration as close to normal as possible, both fasting and postprandially. The primary limiting factor is the frequency of hypoglycemia. We believe that when hypoglycemia is immediately corrected it represents no threat to the fetus; our patients have had no difficulty in recognizing early symptoms.

Two of the patients previously had stillborns, before the diagnosis of diabetes was established. It is obvious therefore, that early diagnosis of diabetes is mandatory. Determination of blood sugar two hours after 100 gm. of glucose taken orally, and glucose tolerance tests, when indicated, have become part of standard prenatal care.

The ultimate goal is early diagnosis of diabetes, and maintenance of blood sugar concentration as close to normoglycemia [50 to 110 mg. per 100 ml. (Somogyi-Nelson)] as possible. This requires close cooperation between the physician and the patient; we have found that this effort is well worthwhile in terms of increased fetal survival and decreased morbidity.

Pediatric Management

The increase in the number of live infants born of diabetic mothers has made the pediatrician and his newborn-nursery staff important members of the team caring for the diabetic mothers and their infants. These infants, as is well known, have varied and unpredictable physiologic problems.[7] The typical appearance of these infants is familiar to us all and has been well described in the following classic by J. W. Farquhar:[8]

"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."

In our group of newborns there were 18 live births, and all 18 infants are alive and normal at the time of this writing. *Table 1* illustrates the wide range of birth weights and methods of delivery in the group. The smallest infant weighed 1,758 gm., and the largest 4,224 gm. A typical bloated appearance was noted initially in 10 infants; 8 were normal in appearance.

After delivery each infant was immediately placed in an Isolette tilted with the head slightly lower than the foot. Suction of the nasopharynx was performed as

Table 2.—*Clinical data of 14 diabetic patients during pregnancy*

Patient	Age, yr.	Duration of diabetes, yr.	Retinopathy, grade	Renal disease present	Edema present	Blood pressure, mm. of Hg
1	36	14	II	None	Toxemia	176/100
2	36	13	II	None	None	100/70
3	32	5	0	None	None	110/70
4 (1)	23	9	0	Infection	None	130/90
(2)	24	10	0	None	None	130/90
5	35	13	0	None	None	110/70
6	19	14	II	None	Grade II	110/75
7	38	21	II	None	None	170/100
8 (1)	18	13	II	None	None	110/70
(2)	19	14	II	None	None	110/70
9 (1)	24	9	0	None	None	110/70
(2)	26	11	0	None	None	110/70
10 (1)	30	10	I	Cystitis	Grade I	110/70
(2)	31	11	I	None	Grade I	110/70
11	28	5	0	None	None	110/70
12 (1)	41	2	0	None	None	110/60
(2)	44	5	0	None	None	110/54
13	37	36	0	None	None	140/70
14	30	3	0	None	None	110/70

*Insulin nomenclature: N = NPH; P = PZI; R = Regular or crystalline; LE = Lente; UL = Ultralente; SE = Semilente.
†This was determined by averaging all blood sugar values during pregnancy. Obviously, the blood sugar value was not determined so often when the diabetes mellitus was well controlled as during intervals of hyperglycemia.
‡Mixture.

Table 2.—(*Concluded*)

Patient	Previous insulin* dose	Highest insulin* dose	Average blood sugar value,† mg./100 ml. (Somogyi-Nelson AutoAnalyzer) Morning	Noon
1	45N	70N	114	131 (seen only in hospital)
2	‡52N12R	‡54N18R	104	127
3	None	None	Glucose tolerance abnormal	
4 (1)	‡44N10R	‡74N10R	107	151
	(Diabetic acidosis; carbon dioxide, 12.9 mEq./l.; blood sugar, 238)			
(2)	‡44N10R	‡74N10R	131	151
5	‡44UL44SE	‡50UL26SE	166	156
6	50N	‡96N20R	116	131
7	30L	‡60LE25SE	128	188
8 (1)	78N	62N	120	105
	(Diabetic acidosis; carbon dioxide, 4 mEq./l.; blood sugar, 571)			
(2)	78N	‡74N6R	102	141
9 (1)	‡50N8R	‡28P108R	135	133
(2)	‡50N8R	‡28P108R	130	135
10 (1)	38N	‡44N5R	159	142
(2)	38N	‡40N5R	155	160
11	‡30LE6R	‡50LE30SE	110	133
12 (1)	None	None	Glucose tolerance abnormal	
(2)	None	None	Glucose tolerance abnormal	
13	36N	‡40UL25SE	138	163
14	None	None	Glucose tolerance abnormal	

needed. No infant required vigorous resuscitation. After 10 or 15 minutes, when the nasopharyngeal airway seemed clear and respirations were regular, a tube was passed to the stomach and the gastric contents was removed by suction. After this initial handling and examination of the infant came a period of close observation. During this period, the Isolette temperature was regulated to maintain the infant's body temperature between 96 and 98 F. Oxygen was not routinely used unless cyanosis developed in the course of respiratory distress. The blood hemoglobin content, hematocrit reading, blood sugar and serum calcium determinations were made of most infants; serum pH and electrolyte values were also measured in some cases.

Oral feedings of Karo-water, 5 to 15 ml. from every one to two hours, were instituted when the infant was able to suck—in from 12 to 60 hours. The infant was not fed until there was evidence that feedings would be tolerated. Early feedings were avoided in infants with respiratory distress, to obviate superimposing the problems of aspiration.

The clinical courses of these infants were unpredictable and varied. Some infants who had a typical appearance had no problems, whereas in others respiratory distress, hypoglycemia, and hyperbilirubinemia developed. *Table 3* lists the problems encountered.

Table 3.—*Problems in offspring of diabetic mothers*

Complications	Appearance	
	Typical (10 infants)	Normal (8 infants)
Hypoglycemia (< 30 mg. after 3 hr.)	2	—
Respiratory distress	6	1
Hyperbilirubinemia (serum bilirubin, > 12 mg. per 100 ml.)	4	3
Convulsions	1	—
Apneic spells	3	—
Hypocalcemia	1	—
None	3	4

Hypoglycemia was not a serious problem and did not seem to be related to the clinical appearance and course of the infant. Most cord blood sugar values were in the range of 10 to 20 mg. per 100 ml., but in from one to two hours later, levels of from 30 to 50 mg. per 100 ml. were found. Two infants had levels below 30 mg. per 100 ml. two hours after birth and were clinically asymptomatic. Subsequent results of blood sugar tests of these infants were in a normal range. No infant received an intravenous injection of dextrose. Glucagon hydrochloride* (300 μg. intramuscularly) was given to one infant who had a convulsion three hours

**Eli Lilly and Company.*

after birth. The blood sugar value at the time of the convulsion was 33 mg. per 100 ml.

The respiratory distress syndrome occurred in six infants, each of whom had the "typical" macrosomia. The management of each one was individualized, but high humidity, oxygen as needed to prevent cyanosis, and injections of antibiotics were the principal forms of therapy. Digitalis was used in two infants with respiratory distress, but did not seem to alter the course.

Hyperbilirubinemia (serum bilirubin concentration more than 12 mg. per 100 ml.) was noted in seven infants. One infant with an associated Rh incompatibility received two exchange blood transfusions.

Lethargy was present in most of the infants. Spontaneous activity in the crib was less than the normal infant's, and the mothers often commented that it was from two to three weeks after discharge from the hospital before the infants exhibited normal activity.

Comment

In the evaluation of the results obtained in this group of 14 diabetic mothers, several important points are worthy of emphasis. Most important is the strict control of the diabetes in patients who are educated to know the effects of pregnancy upon their disease with consequent changes in insulin dosage. The realization that urine sugar determination is not always a reliable index for control has led to an increased use of the *blood sugar determination*. When it appears that acidosis is threatening (particularly when the ferric chloride test for diacetic acid in the urine is positive), as might occur in any infection, early hospitalization is indicated. The only fetal death in this series occurred when a "brittle" diabetic failed to report a severe upper respiratory infection, and arrived in the emergency room in a state of acidosis. We believe that this represented a preventable fetal death. This same patient has since been delivered twice by cesarean section and has two living children.

Delivery between 35 and 37 completed weeks of pregnancy is advocated. There are individual circumstances, particularly the occurrence of preeclampsia, which might alter this decision toward the earlier mentioned week or even before that time. In our experience, this individualization is most important in lowering the incidence of fetal mortality.

It is evident from the report that no single program of management was utilized for the infants. The most important observation is that these infants, though all but two weighed more than 2,500 gm., both clinically and physiologically behaved like premature infants. If this is realized by the physician and the nursery staff, and the infant's care is patterned accordingly, an increased survival rate of such infants will occur. Pediatric principles of premature care are important not only because of the high incidence of spontaneous labor before the thirty-fifth

week, but because application of these methods to all diabetic newborns has contributed importantly to increased survival rates.

Finally, the cooperation of the three involved specialties—obstetrics, endocrinology and metabolism, and pediatrics—with frequent intercommunication regarding specific problems, has made possible a favorable prognosis for infants of diabetic women.

References

1. Plotz, E. J., and Davis, M. E.: Endocrine patterns in pregnant diabetic women. Clin. Obst. & Gynec. **5:** 346-378, 1962.
2. Black, M. E.: Personal communication, Dec. 7, 1962.
3. McElin, T. W.: Mode of delivery—vaginal or cesarean—in diabetic pregnancies. Clin. Obst. & Gynec. **5:** 426-437, 1962.
4. Black, M. E., and Miller, M.: Management of diabetes and pregnancy. Clin. Obst. & Gynec. **1:** 229-244, 1958.
5. White, P.: Pregnancy complicating diabetes, p. 690-716, *in* Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, 10th ed. Philadelphia: Lea & Febiger, 1959, 798 p.
6. De Alvarez, R. R.: Toxemia of pregnancy in diabetic. Clin. Obst. & Gynec. **5:** 393-408, 1962.
7. Gellis, S. S., and Hsia, D. Y. Y.: Infant of diabetic mother. A.M.A. J. Dis. Child. **97:** 1-41, 1959.
8. Farquhar, J. W.: Child of diabetic woman. Arch. Dis. Child. **34:** 76-96, 1959.