FETAL AND MATERNAL MORTALITY IN DIABETES*

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PRIOR to the discovery of insulin, agreement was uniform that pregnancy constituted a dangerous and undesirable complication of diabetes mellitus. The literature before 1923 is filled with discussion and case reports concerning the harmful effect produced by pregnancy. Few diabetic women bore children (pregnancies in 2 per cent, 5 per cent, 6 per cent of diabetic women of childbearing age as reported by Skipper, Van Noorden, Lecorche), but when a patient did become pregnant her diabetes became more difficult to control, she was very likely to develop acidosis and her chances of surviving the pregnancy were much less than for normal women. The likelihood of obtaining a liveborn infant capable of surviving the neonatal period was less than 50 per cent. The cause of the high fetal death rate was due to many factors. Spontaneous abortions in the early months were attributed to an abnormal endometrium, to variations in maternal blood sugar or to ketosis. Therapeutic abortions were necessitated by increased difficulty in controlling the blood sugar level in the presence of pregnancy. Hydramnios was a frequent occurrence (12 of 66 pregnancies in diabetes collected from the literature by Williams in 1909) and was usually associated with death of the fetus (83 per cent of Williams' 12 cases). The excessive development which frequently occurred if the fetus survived until term was responsible for a greater incidence of intracranial injury than occurs in infants of normal size. A higher incidence of malformations in infants born of diabetic mothers was reported by Joslin, but has not been corroborated by other investigators. Ketosis and abnormal products of metabolism circulating in the mother's blood were regarded as frequent causes of intrauterine death. Hypoglycemia after birth, caused by an overly active fetal pancreas, developed in response to low maternal pancreatic function, was considered a frequent cause of death in the early neonatal period.

One of the first large series of cases of pregnancy in diabetes mellitus collected from the literature was reported by Williams in 1909. In this group of 66 pregnancies, 57 occurred in diabetic women and the first symptoms of diabetes developed after conception occurred in 9. Contrary to more recent observations the mortality was higher in the latter group than in the first. Of the 9 patients with the onset

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of diabetes during the pregnancy 3 died in coma shortly after labor, 2 died of coma at one and at four months later, 2 died of malignant tumors shortly after labor. Death from diabetes occurred in 55 per cent. Only 3 infants survived, two from mothers who also survived and one from a patient who died of a brain tumor. In the 26 patients (57 deliveries) in whom diabetes was present before conception the mortality during the puerperium was 25 per cent, during the next two years 20 per cent, with a fetal mortality of 49 per cent. Ten of these patients had more than one pregnancy, 6 being apparently entirely unaffected by repeated pregnancies.

Joslin observed 130 pregnancies occurring in diabetic women before the insulin era. Seventy-one per cent of those proceeding to term, in whom the outcome of the pregnancy was known, resulted in liveborn infants. However, from a total of 115 pregnancies (the outcome was unknown in the other 15) there were obtained only 57 live infants (50 per cent). There were 23 stillbirths, 23 abortions and miscarriages, 5 therapeutic abortions, 7 deaths because of deaths of undelivered mothers. The maternal mortality is given as 5 per cent, all deaths being due directly to diabetes.

Since the advent of insulin many more cases have been reported in which diabetes complicates pregnancy.

Fischer believes this indicates that more diabetic women are becoming pregnant. This belief is supported by Skipper's figures which show that of 367 married diabetic women under forty-six years of age only 2 per cent of 190 observed prior to 1922 were pregnant, while 15 per cent of 177 observed since 1922 were pregnant. In spite of the fact that early diabetes is probably recognized more frequently than it was in the past, these figures show that the fertility of a diabetic woman is probably increased by insulin.

Wilder and Parsons (1928), in their study of the effect of pregnancy on diabetes, state that in their experience no patient is permanently harmed by pregnancy if the disease is properly treated. They report 9 cases of pregnancy in diabetes with 6 living children (66⅔ per cent). The deaths include one infant stillborn at term in a case of neglected diabetes, and 2 abortions at two and seven months from coincidental causes. There was no maternal mortality. An investigation of 51 published case histories from 1923 to 1928 shows 57 per cent living babies with a maternal mortality of 13.7 per cent (7 deaths).

Skipper (1933) reports 37 pregnancies in 33 women with a fetal mortality of 40.5 per cent (including 3 therapeutic abortions), with no maternal mortality during labor or the puerperium and with but one death inside of two years. His figures, collected from the literature on 136 pregnancies in 118 women, show a fetal death rate of 45.2 per cent (abortions, stillbirths, neonatal deaths) and a maternal death rate of 9.3 per cent during pregnancy or the puerperium, with an additional 3.4 per cent dying within two years after delivery.

Ronsheim, between 1920 and 1933, observed 36 pregnancies in diabetic women with only 13 live births (36 per cent), the deaths including 8 therapeutic abortions, 13 stillbirths, and 2 miscarriages. There was only one maternal death. He states that uncontrolled diabetes invariably results in miscarriage, premature birth, or death in utero a few weeks before term. Cesarean section a few weeks before term may occasionally be indicated in the interest of the patient.

Duncan and Fetter (1934) report 6 pregnancies in 5 diabetic women with no fetal or maternal mortality.

Kramer (1935) in 17 patients with 20 pregnancies observed no maternal deaths during pregnancy or the puerperium and only one within two years. He states

there were 5 abortions, including 2 therapeutic, but does not give the number of live births. He has collected 238 cases from other authors in which there were only 114 infants alive three days postpartum (50 per cent). There were 8 maternal deaths during the puerperium, 17 within one year and 19 up to three years, making a total of 14.2 per cent.

Joslin's series of cases (1935) is the largest reported by a single investigator since insulin has been available and consists of 122 pregnancies in which the outcome is known. In only 57 per cent of the cases did the fetus survive. If 13 therapeutic abortions are excluded, the percentage rises to 70 per cent (live births 70, stillbirths 19, miscarriages or abortions 19, therapeutic abortions 13, ectopic pregnancy 1). In 73 patients under Joslin's immediate care the number of live births is 68 per cent, or 75 per cent if 7 therapeutic abortions are excluded. The maternal death rate of 5 per cent is the same as in the pre-insulin era but the cause of death has changed from diabetic coma to obstetric complications. He believes that cesarean section in the early part of the eighth month is the ideal method of delivery.

Since the opening of the present Chicago Lying-in Hospital at the end of May, 1931, until Oct. 1, 1936, 16 pregnancies in 15 women having proved diabetes mellitus have been observed. There have been a total of 14,464 deliveries during this period, making an incidence of approximately one in every 900 deliveries. Eleven women had had symptoms of diabetes for at least two years before the onset of pregnancy, in three it developed during the course of the pregnancy, and in one case the time of onset was unknown. There was only one maternal death (6.6 per cent). This occurred in a woman admitted to the hospital in coma, who had had no prenatal care and who died undelivered a few hours after admission. There were 11 infants (68.7 per cent) alive at the end of the neonatal period. The fetal deaths were due to one therapeutic abortion performed because of the acidosis produced by hyperemesis gravidarum; to one delivery of a macerated stillborn infant in a woman with poorly controlled diabetes; one premature onset of labor at thirty-one weeks due to an unknown cause in which the infant succumbed six hours after delivery, one death of an undelivered infant, and to one death of an infant showing evidence of antenatal pneumonia as a result of premature rupture of the amniotic membranes.

In general, the age when pregnancy occurred is slightly greater than usual, the average age in this group being thirty years. Seven women (50 per cent) showed evidence of toxemia, 5 having relatively mild symptoms and 2 having very severe symptoms. Delivery was natural or aided by low forceps in 7, accomplished by cesarean section in 5; one patient died undelivered and one was subjected to a therapeutic abortion. In the 5 patients delivered by cesarean section the diabetes was considered sufficiently severe to warrant sterilizing the patient at the same time.

The mean weight of the infants delivered at term was 3,935 gm., and the sexes were equally divided. There were no fetal malformations.

The patients were all carefully observed during pregnancy and were, with one exception, very cooperative. The one patient who was delivered

of a macerated infant found it very difficult to adhere to an accurately planned diet because of financial embarrassment. With the exception of two patients insulin was given during all or the greater part of the pregnancies.

DISCUSSION

Since the advent of insulin the entire management of diabetes has changed. It is no longer invariably fatal even when the onset of the disease is in childhood. The surgical risk to the patient has been markedly lowered, and the average diabetic patient who follows the advice of a competent physician has a life expectancy not greatly below that of the nondiabetic individual. The diabetic patient's reaction to pregnancy must necessarily also be modified by the present accessibility of insulin.

The varying nutritive requirements during pregnancy make it imperative that a diabetic patient be more closely supervised than is otherwise necessary. If her blood sugar level is not constantly controlled by diet and insulin, her outlook is no better than it would have been in the preinsulin period. Hyperemesis gravidarum may make it impossible to prevent acidosis in a diabetic patient and is a more serious complication than in a nondiabetic. This is one of the few conditions in diabetes in which therapeutic abortion may be necessary.

The published opinion of various writers differs as to the possible effect of pregnancy on the mother, but from a careful study of many of the cases reported, it seems warranted to draw the following conclusions. Pregnancy constitutes an additional strain on an organism already handicapped by an abnormal sugar metabolism. As in any disease, unnecessary additional factors constituting in themselves a risk to the patient are to be avoided if possible. For this reason, if no other conditions are taken into account, pregnancy is to be avoided. If, on the other hand, the patient is anxious to bear children and is able to have her dietary and insulin requirements carefully controlled, there is no evidence to indicate that she will be certainly and permanently harmed by the pregnancy. Death from coma, which was the usual cause in preinsulin days, is extremely uncommon. (Joslin observed none in 138 pregnancies.) There is a slightly greater risk of toxemia or eclampsia occurring, for the incidence is higher in diabetic than nondiabetic patients, but appropriate treatment may be instituted. Here, as in all patients, careful observation and the discovery of the impending toxemia is the important factor in preventing casualties.

The number of fetal deaths in the series of cases compiled from the literature remains high (see Table II). This is partly due to the inclusion in the statistics of all abortions and miscarriages both uninten-

tional and therapeutic. Adair and other investigators have found that among women in general approximately one-third of all pregnancies end in abortions. The incidence is not greater than this in diabetes, so although we may in this group ascribe a reason for the abortion where ordinarily it is very difficult, the incidence in general is no higher than among women in the nondiabetic group.

TABLE II. PUBLISHED MATERNAL AND FETAL MORTALITY RATES IN DIABETES MELLITUS

	YEAR PUBLISHED	NUMBER PATIENTS	NUMBER PREGNANCIES	*FETAL MORTALITY %	MATERNAL MORTALITY PER CENT		
					DURING LABOR	FOLLOWING 2 YEARS	TOTAL
Williams	1909	43	66	49.0	25.0	20.0	45.0
Joslin	1935[1]		115	50.0	5.0		5.0
Parsons and Wilder	1928	9	9	33.0			
Parsons and Wilder†		43	51	47.0			12.0
Skipper	1933	33	37	40.5		3.03	
Skipper†		118	136	45.2	9.3	3.4	12.7
Ronsheim	1933		36	64.0	2.8		2.8
Duncan and Fetter	1934	5	6				
Kramer	1935	17	20			5.0	5.0
Kramer†			238	50.0			14.2
Joslin[2]	1935		122	43.0			5.0
Chicago Lying-in Hospital (present series)	1936	15	16	31.3	6.6		

*Includes abortions both spontaneous and therapeutic, stillbirths and deaths during neonatal period.

†Cases collected from the literature by the author.

[1]Cases observed prior to the use of insulin (1922).

[2]Cases observed from 1922 to 1935.

If the deaths of previable fetuses are excluded in the Chicago Lying-in series, there are only 3 deaths in 14 pregnancies, a mortality rate of 21.4 per cent. In 81 patients under Joslin's immediate care, 88 per cent of infants delivered at term were liveborn.

In the infants surviving until term the outcome depends largely on the degree to which the maternal diabetes has been controlled. If the patient's urine has been kept relatively sugar-free by diet and insulin and acidosis has not occurred, a live-born infant, within normal limits of size, will probably be delivered naturally. If the diabetes has not been controlled, the outlook is the same as it was in the pre-insulin era; the infant may succumb before delivery and may show maceration of varying degree, it may attain an abnormal size and die as a result of birth trauma, or it may be apparently normal at the time of delivery and succumb soon afterward. Death shortly before labor is probably due in the majority of cases to transmission from maternal to fetal circulation of abnormal metabolic products which interfere with the normal physiology of the infant. Abnormal size of the infant is believed due

to the increased amount of available food material occasioned by the maternal hyperglycemia. Fischer (1935), in analyzing birth weights of 49 infants born of diabetic mothers prior to 1922, found 26 (53 per cent) weighing over 4,500 gm. In 31 infants born of diabetic mothers treated with insulin, there were only 5 which weighed 4,500 or more grams (16 per cent). In none of the patients was pregnancy prolonged. (Kaern, in analyzing 26,644 unselected births, found an incidence of only 0.92 per cent with a birth weight over 4,500 gm. and in half of these the period of gestation was over 291 days.) In all infants over 4,500 gm. the death rate is considerably higher than in those whose weight is within normal limits.

Hypertrophy of the islands of Langerhans in the fetal pancreas, caused by insufficiency of maternal insulin, has been reported by several investigators (Gordon, Heiberg, Skipper, Dubreuil and Anderodias, Feldman, Ambard, Wiener). Whether or not insulin passes through the placenta into the maternal blood stream and thereby partially compensates for the lack of insulin in the maternal organism has not been definitely proved. The hypothesis that after birth the excess of insulin, no longer being able to escape through the placental circulation, is sufficient to cause hypoglycemia and death of the fetus is an interesting possibility. It is almost impossible to estimate accurately the island tissue in the fetal pancreas. In one case discovered by us in routine autopsy investigation, the fetal pancreas was composed largely of islands, all of which were several times the normal size. The infant succumbed from pneumonia and the mother showed no evidence of diabetes.

Positive knowledge as to the cause of death in the infants born of diabetic mothers is still lacking. This is partly because any investigator has the opportunity of studying only a limited number of cases, and partly because the cause of death is largely from physiologic disturbances and does not produce demonstrable pathologic lesions.

As the general care of the diabetic patient is improved, the fetal death rate will decrease correspondingly. The diabetic woman's chances of becoming pregnant, of having an uneventful pregnancy and delivering a normal child have been greatly increased by the use of insulin. The more nearly normal her metabolic processes can be made the more normal will be her course and the better the prognosis both for her health and that of the infant.

CASE HISTORIES OF PREGNANT DIABETIC WOMEN TREATED AT THE CHICAGO LYING-IN HOSPITAL

CASE 1.—(47668) Patient, aged twenty-seven, para i, gravida ii. Normal pregnancy in 1925 with first symptoms of diabetes in 1926. Insulin requirement both before and during pregnancy varied greatly from time to time with a maximum dose of 70 units daily. Delivery at term of a 3,010 gm. female infant by cesarean section with accompanying sterilization Nov. 9, 1931. Complication: moderate hypertension. Mother and infant discharged in good condition.

CASE 2.—(59732) Patient, aged twenty-three, para i, gravida ii. Pregnancy in 1929 complicated by eclampsia with spontaneous delivery of thirty-seven weeks' fetus which died shortly after delivery. First symptoms of diabetes occurred six months later since which time she has been on a moderately restricted diet and an average of 50 units of insulin daily. Insulin requirement varied practically none during pregnancy. She was given a five-hour test of labor at term but since progress was not satisfactory she was delivered by cesarean section with accompanying sterilization on Aug. 26, 1932. Infant, male, 4,550 gm., normal. Complications: yeast infection, hydramnios, severe preeclamptic toxemia.

CASE 3.—(55029) Patient, aged thirty, para 0, gravida i. Onset of diabetes in 1927, controlled by diet and an average insulin intake of 30 units daily. When six months pregnant, insulin requirement was 90 units daily, at time of delivery 45 units. Delivered naturally June 30, 1932. Normal female infant, 4,015 gm. Mother and infant discharged in good condition.

CASE 4.—(65599) Patient, aged thirty-six, para iii, gravida iv. Pregnancies in 1917 with 3,800 gm. liveborn infant, 1926 with 5,800 gm. stillborn infant, 1930 with 4,500 gm. liveborn infant. Onset of diabetes in 1923. Disease controlled largely by diet with only occasional use of insulin. First seen Aug. 17, 1932, when four months pregnant. Impossible to control diabetes adequately because of lack of cooperation of patient. Delivered naturally of a 3,945 gm. macerated female infant on Feb. 19, 1933.

CASE 5.—(97804) Patient, aged thirty-six, para iv, gravida vi. Four normal liveborn infants; 1913, 2,700 gm.; 1916, 4,500 gm.; 1918, 3,600 gm.; 1922, 3,500 gm.; unintentional abortion at six weeks in 1933. First symptoms of diabetes in July, 1932, controlled by diet until July, 1933 when started taking 30 units of insulin; 65 units in January, 45 units in February, none by the end of March. Delivered naturally Apr. 18, 1934. Normal female infant, weight 4,000 gm. Insulin requirement 15 units daily following delivery until became pregnant again. At eight months required 60 units, at nine months 25 units, at time of delivery none. Delivered on Nov. 8, 1935, by cesarean section. Sterilized. Normal male infant, weight 4,685 gm. Complications of both pregnancies: syphilis, obesity, hypertension; of the second only, preeclampsia, yeast vaginitis.

CASE 6.—(106230) Patient, aged thirty-eight, para i, gravida vii. One normal delivery of 5,000 gm. liveborn infant in 1915 followed by 5 unintentional abortions. First seen June 14, 1934, when sugar was discovered in the urine. Sugar tolerance curve showed presence of diabetes mellitus. Blood sugar was controlled by diet of carbohydrate 110, protein 65, fat 100 without the use of insulin. Delivered naturally at term on Aug. 16, 1934, of a 3,610 gm. normal female infant. Complication: mild toxemia. Mother and infant discharged in good condition.

CASE 7.—(112772) Patient, aged twenty-two, para i, gravida ii. One normal delivery in 1931. First seen on admission to the hospital when six months pregnant Sept. 20, 1934, with history of continuous vomiting and absence of fetal movement for five days. Blood chemistry on admission was nonprotein nitrogen 107, chlorides 438, sugar 322, CO_2 combining power 25 volumes per cent. Diagnosis made of diabetic coma. Died undelivered twenty-four hours after admission. Had had no prenatal care and there had been no previous diagnosis of diabetes. Autopsy confirmed diagnosis.

CASE 8.—(99543) Patient, aged twenty-six, para 0, gravida ii, one unintentional abortion in 1930. Onset of diabetes in 1928; controlled by diet and an average of 10 units of insulin daily. Tolerance remained practically stationary during preg-

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