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Newborn infant of a diabetic mother

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THE NEWBORN INFANT OF A DIABETIC MOTHER

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INTRODUCTION

The objectives of this thesis are twofold:

(1) A review of the literature concerning this subject, and,

(2) To determine the effects of maternal diabetes on the newborn baby.

No attempt will be made to cover the vast field of diabetes complicated by pregnancy, about which a great deal has been written. The maternal aspect of this subject will be touched upon only when necessary for sake of completeness. The fetus is mentioned from time to time because of the intimate developmental relationship to the newborn.

The general historical background will be discussed briefly, so as to present the situation as it was before and after the discovery and therapeutic use of insulin.

The general physical characteristics of the newborn of a diabetic mother are discussed, including size, weight, cardio-respiration status, condition of the body tissues, viscera, laboratory studies, etc.

Morbidity in such infants is considered, discussing such factors as respiratory difficulty and

its causes, traumatic injuries due to difficult delivery, cardiac hypertrophy, blood sugar levels and congenital anomalies.

Mortality among the newborn babies of diabetic mothers is investigated from a standpoint of etiology. Factors such as, toxemia, bouts of keto-acidosis, premature delivery, to difficult and prolonged labor, abnormal hormonal balance in the mother, and other existing theories are considered. Statistical data also will be included.

Autopsy findings, while rather meager, will be presented, demonstrating abnormal findings in such tissues as the lungs, heart, liver, pancreas, and nervous system.

This thesis will not be concerned with the treatment or control of the maternal diabetes, nor will it include to any extent the care and treatment of the newborn.

The material for this subject, while interspersed and hidden in numerous writings, has proven to be very fascinating. Few articles have been written concerning this subject directly, most having been found in conjunction with work on pregnancy and diabetes.

There is no original work presented in this thesis. It is merely a review of the existing and current literature, and an attempt at correlating the works of several authors.

It is the aim of this writer to cover this material adequately yet briefly as possible.

General Historical Background of Pregnancy Complicating Diabetes

Pre Insulin Era

Prior to the advent of insulin in 1921, most women suffering from diabetes mellitus were sterile. The incidence of genital hypoplasia and amenorrhea also was high. Pregnancy, when occurring, constituted a dangerous and undesirable complication of diabetes. Duncan, in 1882, was able to find only thirteen cases in the literature and added three of his own.

The cause of infertility in diabetic women was not well understood. One theory advanced was that it was due to hypofunction or hyperfunction of the anterior pituitary gland. This abnormality gave rise to disturbances of the generative tract, such as, disappearance of Graafian follicles, atrophy of the uterus, lack of development of the genital tract (White), and amenorrhea. Because of restricted diets and reduction in essential food elements, Eastman postulates that nutritional deficiences may have been a contributing factor as to etiology of sterility, in addition to endocrine imbalance.

Zilliacus states there were three main problems which characterized the pre-insulin period:

(1) Low fertility among diabetics

(2) High maternal mortality

(3) High fetal mortality

Low fertility was common, LeCorche in 1885 and Skipper in 1933, reported only 2 to 6% of diabetic women became pregnant.

Maternal mortality was quite high, some authors, such as Williams (1909) report 25-35% of pregnant diabetics died during parturition or within two weeks of it, and a further 23% died during the following two years. Skipper reported a lower rate, 9.3% during pregnancy, parturition or the puerperium, and another 3.4% died within the following two years. Joslin in his series had a maternal mortality rate of 5%, all of which were due to diabetes mellitus.

The fetal mortality rate in the pre-insulin era was also very high. Joslin in his study of 115 pregnancies obtained only 57 live infants, which represents a mortality rate of 50%. Potter and Adair state that the likelihood of obtaining a live infant capable of surviving the neonatal period was less

than 50%. Eastman reports a 50% fetal mortality rate. He also cites the series of Duncan and Williams in which the mortality was 47 and 41% respectively.

Eastman makes an interesting statement in regard to the diabetes and pregnancy, which is quoted, "the experience of the pre-insulin era, as surveyed above, is not merely of historical interest but is of great clinical importance, because it shows that untreated diabetes and pregnancy are basically incompatible".

Without insulin, diabetes was very difficult to control, and even more so when aggravated by pregnancy often to a fatal degree.

Post Insulin Era

Maternal Mortality Rate

Since the introduction of insulin therapy the maternal mortality rate has been reduced to an almost negligible figure. The mortality rates reported by many workers illustrate this statement. In 1946 White found the maternal mortality rate to be reduced to 0.46% among 271 cases of pregnancy and diabetes.

Other figures range from 0 (Herrick & Tillman, 1938) in a series of 67 pregnancies,to 7% (Potter & Adair, 1936) among 15 patients and 16 pregnancies. These maternal mortality rates indicate the importance of insulin therapy in diabetes complicated by pregnancy. The most significant factor is the control of the diabetic condition. Almost all maternal deaths today from diabetes complicated by pregnancy are due to neglect.

It has been very interesting to note, in the review of the literature, that while the maternal mortality has been substantially decreased, the fetal mortality rate, by contrast, remains quite high in spite of insulin therapy. This presents a serious problem because of the increased number of diabetic women who are becoming pregnant. Regardless of insulin therapy the incidence of spontaneous abortion, premature birth, toxemia, fetal death in utero, abnormally large babies, polyhydramnios and congenital malformations is high.

Incidence

White, in 1935, estimated that there were over 100,000 prospective diabetic mothers in the United

States. No doubt this figure is larger today. Harris & Fisichella in 1950, also estimated that there were approximately 100,000 female diabetics of the child bearing age in the United States alone. They state that of this number 10,000 will have pregnancies and of the 5,000 expected living births, 500 will succumb two months prior to term, 510 are liable to die in the first 24 hours of life, and 1,250 are liable to develope diabetes mellitus later in life.

Race

Joslin found that diabetes in the childbearing ages was 100% more prevalent in the colored race. However this was not true in the work of Rike & Fawcett, who found diabetes complicating pregnancy was two times as prevalent in the white as in the negro.

No other data on race was found in the literature.

Age

It is a well known fact that the incidence of diabetes mellitus increases sharply with age. The

maximum susceptibility to the development of the disease is not reached until the mid fifties. From the statistics of the National Health Survey, Joslin shows that in females between 15 and 24 years of age the frequency is 1:1700; between 25 and 34, 1:900; between 35 and 44, 1:300; between 45 and 54 1:125; between 55 and 64, 1:50 and in women 65 and over, 1:45. According to Eastman these figures explain the relative infrequence of diabetes in pregnancy. Also that when encountered, the chances are greatly in favor of its being met in older women and as a result other complications are more frequent, especially hypertension.

It is the finding of almost every author that the average age of the pregnant diabetic is greater than that of the non-diabetic patient. Below is a table constructed to show average age in the series of several authors.

Table I

Average Ages in Pregnant Diabetic Patients

Author	Average Age	
	Diabetic	Non Diabetic
1. Rike & Fawcett (1948)	31 yrs.	23 yrs.
2. Given, Douglas, and Tolstoi (1950)	30.2 yrs.	-
3. Paton	33 yrs.	-
4. Frankel	32 yrs.	23 1/2 yrs.
5. Harris & Fisichella	28 yrs.	-
6. Bill & Posey	Average age for diabetic same as for the non diabetic.	
7. Lavietes	Average age increased.	

Frankel advances three theories as to cause of advanced maternal age: (1) contraception practiced because of fear of the offspring inheriting diabetes (2) late marriages and (3) avoidance of gestation because of fear of pregnancy and its complications.

III

General Physical Characteristics of the Newborn of a Diabetic Mother

General Appearance

The infant of a diabetic mother frequently, on inspection, appears to be fat, edematous, sluggish, cries and breathes poorly, does not feed well and often is jaundiced.

Size and Weight

It is generally agreed, almost without exception, that the infant of a diabetic mother is of greater size and weight than that of a non-diabetic mother. There is little data available as to the length of these infants, however Harris & Fisichella found in a series of eight such infants, 50% were 50 centimeters or more in length at birth. Mitchell & Nelson report the normal full term infant is 48 centimeters or over, crown - heel length. Zilliacus, in 10 infants of diabetic mothers found the height to be considerably above the normal, attributing this to increased growth. Sisson in his series found no evidence that the skeleton was larger, and attributed

the increased weight to obesity. It is the opinion of White that the increased weight is contributed to by three factors, namely (a) obesity, (b) edema and (c) splanchnomegaly. White believes the nutritional potentialities of the maternal diabetic blood are greater than those of the normal, and observed the excellent nutritional level of these infants to be evident on simple inspection. As evidence for edema causing an increase in weight, she found it to be visible in many, pitting on pressure, and also by the weight loss, in a great many of the 125 studied, due to diuresis. In a period of 72 hours, the weight loss varied from less than the normal of 1/10 of an ounce up to 25 ounces. White reports a weight loss of exactly one pound in 12 hours in a 7 pound infant. Let it suffice to say at this point that splanchnomegaly is a third factor in increased size and weight. This factor will be discussed at length later in this thesis. Such authors as Gonce, Lawrence and Oakley, Zilliacus, Potter and Adair, Sisson, Given, Douglas and Tolstoi, and the majority of others are in agreement with White as regards the excessive size of the infant

of a diabetic mother. White found in 1947 that 80% of the infants of diabetic mothers exceeded the normal weight for the period of gestation.

The underlying basis or etiology for the increased size and weight is not clearly understood and is of a controversial nature. An older, well accepted conception, and still advanced by Lawrence and Oakley and Potter and Adair, is that the incidence of "giant" babies in diabetic pregnancies is due to excessive supplies of sugar reaching the fetus as a result of maternal hyperglycemia. They feel that if diabetes is controlled, urine kept relatively sugar free, and acidosis has not occurred, a live infant within normal limits of size will probably be delivered naturally. This is partially true, according to White, insofar as obesity is concerned. Given, Douglas and Tolstoi found no evidence that a high blood sugar was conducive to an oversize baby and say there is considerable evidence against this hypothesis. The work of White and others is cited in which attempts to maintain normal blood sugar was made and yet large babies were observed. They also state that large babies are born to pre diabetic mothers in which

there was no glycosuria nor hyperglycemia at time of birth. Miller, Hurwitz and Kuder's findings are similar in that they believe that infants with a birth weight of 5 kilograms or more are born to women before they become diabetic with the same high frequency as after diabetic symptoms have appeared. Allen also has shown that large babies are born to diabetic women during the 5 years immediately before the disease develops. The theory of hyperglycemia as a cause for excessive size is discounted by Allen. Bill and Posey in their series had large infants from mothers whose hyperglycemia was mild to the degree that it was controlled by diet alone.

Another theory advanced, for the etiology of excessive sized infants, which appears to be gaining favor, is that of hormonal derangement. This theory has for its basis the experimental work of Snyder in 1934 and Hooper in 1934. By injecting prolan into pregnant rats and rabbits they were able to produce overdeveloped, macerated offspring in which an autopsy revealed the over weight to be due to obesity, edema and splanchnomegaly. White, because of the high incidence of toxemia in pregnant diabetics has determined

levels of chorionic gonadotropin, estrogen and progesterone in these women. She is of the opinion that the gigantism may be a result of excess chorionic gonadotropin, citing the experimental work of Snyder. Eastman doubts this possibility and states that the large macerated fetuses of experimental animals were due to prolongation of pregnancies with continued growth for at least three days beyond term. In contrast to this he states that the giant fetuses of human diabetics are not the result of prolongation of pregnancy, as they are encountered before term. It is also postulated that chorionic gonadotrophin produces giant fetuses through the production of additional progesterone from fresh corpora lutea. This is the substance recommended by White for the prevention of giant fetuses according to Eastman. In spite of the ideas above, White, Titus, Joslin and Hunt in 1939, observed that the weight of the babies in a series of diabetic pregnancies treated with estrogens and progesterone was within normal limits. White's findings of decreased serum levels of estrogen and progesterone and increased serum chorionic gonadotrophin have been duplicated by Gonce, who

also holds the abnormal endocrine balance responsible for the complications of pregnancy and the pathological changes in the offspring. After reviewing the literature, it appears probable to this writer that abnormal endocrine balance is definitely a factor in the production of large infants of diabetic mothers. This factor in addition to hyperglycemia in the mother and resultant increased nutrition.

Allen, (1939), Miller, Hurwitz and Kuder, (1944), and others revealed that mothers, who later were found to have diabetes mellitus, often gave birth to large overweight infants. Zilliacus suggests, on the basis of this work, that the hypophysis is involved. He postulates that the diabetogenic principle may have a growth promoting effect which possibly manifests itself in the form of overdeveloped fetuses even during the pre-diabetic period. This obviously would not be affected by well balanced insulin treatment.

From the above discussion it is evident that almost all investigators agree as to the increased size and weight of infants of diabetic mothers, but are not in agreement as to the underlying cause. Considerable work remains to be done before this problem is settled.

Statistical Data - Weights of Infants of Diabetic Mothers

The following data, as reported by various authors, is given in evidence of the increased weight in infants of diabetic mothers. The average weight for full term white infants (of non-diabetic mothers) is 3,224.6 grams or 7.1 pounds and slightly less for negroes - according to Given, Douglas and Tolstoi.

Lawrence & Oakley - Average weight of live babies - 8 pounds 8 oz. to 12 lb. 6 oz. Series included 52 babies, 27 weighed 9 lb. or more, of which 7 weighed between 10 - 11 lbs. 6 equalled or exceeded 11 lbs. heaviest was 12 lb. 6 oz.

Zilliacus - Reports a series of 10 babies, several weighed over 6,000 grams. 3 greatly above normal - 6,450, 5,480 and 5,450 grams.

Potter and Adair - Mean weight of infants at term was found to be 3,935 grams.

Lavietes, Leary, Winkler and Peters - Average birth weight of 12 babies - spontaneous labor - 3,860 grams. Average in 24 babies, 12 of which were induced prior to term was 3,636 grams.

Given, Douglas and Tolstoi - 52% of babies weighed 8 lb. or more (3,636 grams)

7.2%	weighed	0 - 6 lb.
14%	"	6 - 7 lb.
26.5%	"	7 - 8 lb.
25.8%	"	8 - 9 lb.
20%	"	9 - 10 lb.
6%	"	10 lb. or more.

Miller, Hurwitz and Kuder report:

17	births	- weighing	1.0 - 2.5 kg.
40	"	"	2.5 - 3.5 kg.
57	"	"	3.5 - 4.5 kg.
29	"	"	4.5 - 6.0 kg.

These authors found the incidence of babies who weighed more than 5 kg. at birth was 3.9% before diabetes was diagnosed in the mother and 6.4% after the onset.

Paton - Reports 21 of 38 babies or 55% weighed 8 lbs. or more. Of the 21, 5 weighed 10 - 11 lbs., 1 weighed 11 - 12 lbs. and one over 13 lbs. (According to Allen, Randall and Rynearson only 9% of normal pregnancies will produce babies weighing 8 lbs. or more.)

Frankel - Records weights of 17 babies, eleven of which exceeded 8 lbs. Average weight was 8.2 lbs.

Harris & Fisichella - Of 18 babies, 3 weighed over 4,200 grams, 9 ranged from 3,100 to 3,700 grams.

Bill & Posey - Found 20% of their series weighed over 4,000 grams.

Wilson - Reports 18 of 41 babies with a weight of 8 lbs. or more.

Rike & Fawcett - Average weight of 22 babies, or 42.3% of their group delivered at term, was 8.27 lbs. Range was 6 lbs. - 11 lbs. 2 oz. Found that the weights of the 8 and 8 1/2 month pregnancies conformed more closely to those of the average normal term infant. Average weight of 8 1/2 month babies was 7.2 lb., of 8 month babies, 7.1 lb.

White - has reported a birth weight above normal for the time of gestation in 80% of her series.

The above authors are by no means all that have reported on weights of infants of diabetic mothers, but is sufficient to demonstrate, rather conclusively, that weight is increased in such babies.

Condition of the Heart, Lungs, Liver, Spleen, and Other Body Tissues.

In examining the newborn of a diabetic mother, the finding of enlarged heart, liver and spleen, as well as atelectasis, is quite common.

A most interesting piece of work was done by Miller and Wilson in 1943, in which roentgen studies were made of hearts of infants of diabetic mothers and compared with those of normal infants, which served as controls. A cardio-thoracic ratio of 55 or greater was arbitrarily accepted as evidence of cardiac enlargement. All x-rays were taken within the first 10 days of life. The studies of the control group were made on the same day of life as for the corresponding infant in the "diabetic" group. The results of this study revealed that in only 4 instances of 17 examinations did the ratio exceed 55 in the control group. Whereas in the diabetic group

ratios greater than 55 were observed in 20 of the 21 examinations.

Another significant finding of this experimental work was that there was a definite trend in the 10 day period for the heart size to decrease. In follow up examinations it was found that within six weeks of life the hearts of all infants had returned to normal size.

Numerous other workers have made similar observations, such as, Gonce, White, Sisson, Given, Tolstoi and Douglas. Gonce found the heart, liver and spleen to be enlarged in many of his cases. He also noted jaundice and atelectasis. All of these, he believes are due to hormone imbalance. Lawrence & Oakley observed that in some infants, although delivered 2 to 4 weeks before term, had reached what appeared to be maturity. Maturity being based on the general appearance of the body and degree of development of the nails. In one of their neo-natal deaths, 24 hours post partum, the brain was edematous with hemorrhages, death being due to asphyxia. Another death, in their series, was due to atelectasis 10 hours post operative. White found splanchnomegaly in a majority of new

cases, the liver, heart and spleen being especially large. She also reports jaundice which appears benign without anemia, which she states is an almost universal occurrence in the infants of diabetic mothers. She further states that atelectasis occurs in varying degrees dependent on prematurity. Bone and gonad development appeared to be advanced in these infants. Enlargement of the pancreas, thymus, and adrenal was seen but not so constantly as that seen in the heart, liver and spleen. In contrast to the enlargement of the above mentioned organs, the brain was consistantly smaller than normal.

Autopsy Findings in Infants of Diabetic Mothers

Some autopsy findings have already been mentioned in the preceding discussion on body tissues. Additional post mortem observations will be presented at this point.

General Appearance - Almost without exception moderate to extensive edema was noted. Some authors, Gonce, White, Given, Douglas and Tolstoi, and others reported jaundice.

Lungs - Given, Douglas and Tolstoi in examination of 13 infants at autopsy found atelectasis, bronchopneumonia, sub-pleural or pulmonary hemorrhage or a combination of the three in 12 cases. In White's report, 1943, there was atelectasis in 18 of 17 autopsied infants. Sisson noted that primary atelectasis was frequent in his 10 infants.

Heart - Enlargement of the heart was frequently noted, being described as hypertrophy in a smaller number. The average weight of the heart of newborn infants has been given as between 20 - 25 grams. Miller and Wilson found the hearts of 9 infants, in a series of 18, to be greatly enlarged, ranging in weight from 32 - 70 grams. Two hearts weighed two times the normal and two weighed three times the normal.

Liver - In the series reported by Given, Douglas and Tolstoi, 9 infants showed abnormal changes in the liver. In 6, enlargement and fatty degeneration was present, focal necrosis in one, and more than the average number of areas of erythropoiesis in 5. Excessive hematopoiesis was a rather common finding of the investigators (Miller and Wilson).

Pancreas - In 7 infants, reported by Given, Douglas and Tolstoi, the pancreas on examination showed hypertrophy or hyperplasia of the Islets of Langerhans. Two showed dilation of the ducts, acute pancreatitis was demonstrated in one. Hyperplasia of the islets was found by White in 5 of 17 autopsied infants. The same observation was made by Hultquist, Ludgren and Dolgaard in 1946. This is also confirmed by Skipper, Weiner, Potter & Adair, Sisson, Miller & Wilson, and Bill & Posey.

Nervous System - Given, Douglas and Tolstoi report some form of intra-cranial hemorrhage in 8 of the 12 infants. In two of these infants tentorial tears were demonstrated. As noted before Lawrence and Oakley found edema of the brain with hemorrhages due to asphyxia. Sisson reports one fatality with cerebral hemorrhage and a tentorial tear.

Kidney - Kidney - Three authors reported persistance of fetal glomeruli in six cases.

Spleen - Excessive hematopoiesis was found by various investigators with about the same frequency as that found in the liver.

Blood Studies on Infants of Diabetic Mothers

Blood Sugar Levels

It is generally agreed by most investigators, that shortly after birth, within 3 to 6 hours, there is a fall in the blood sugar level. This fall is followed by a spontaneous, self correcting, gradual rise and is usually stabilized by the third day of life. This is noted in normal infants as well as in infants born of diabetic mothers. The blood sugar level given for normal infants is 55 to 75 mg.%, for the first two days after an initial drop, rising to higher levels on the third day. There is a difference in the findings of various authors, however, as regards blood sugar levels in infants of diabetic mothers as compared to normal infants. Some workers, notably

Gonce, found that blood sugar levels, in infants of both normal and diabetic mothers, was about the same as that of the mother at birth, decreasing within 3 to 6 hours and rising to 40 to 75 mg.% in the first two days of life. No difference between the normal and the "diabetic" infants was noted. In contrast to this are the findings of White and Sisson. White found that one of the chemical characteristics of the newborn of a diabetic mother is instability of the blood sugar. Initial hyperglycemia followed by a relative hypoglycemia and spontaneous rise in blood sugar level to a normal level for a newborn infant, namely 40 to 60 mg. within 8 hours. It was her impression that the blood sugar was higher than normal, her range being 20 to 250 mg.%. Sisson, in his work, observed that the average blood sugar levels during the first 12 hours were much above the level usually described as normal for an infant of this age. His maximum blood sugar levels ranged from 260 mg.% in four hours down to 170 mg.% from four to eight hours. The average blood sugar levels were 104.5 mg.% up to four hours, down to 79.2 mg.% in four to eight hours and up to 89.2 mg.%

in eight to twelve hours. The minimum level ranged from 30 mg.% up to four hours, 30 mg.% in four to eight hours and 9 mg.% in eight to twelve hours. It was his conclusion that infants of diabetic mothers showed high blood sugar levels, that hypoglycemia was rare and might occur only if mother was given insulin before delivery. The results of Given, Douglas and Tolstoi parallel to some extent those of Gonce. Their normal newborn babies were found to have a wide range of values of blood sugar, 0 to 100 mg.%. The range in infants of diabetic mothers was found to be similar. Miller & Ross report six infants with very low blood sugar levels. In one case, the blood sugar level ranged from zero at 38 hours to 0.026% on the second day to 0.075% on the eighth day. Another case had a blood sugar of 0.102% at 45 minutes of age, less than 0.010% at 3-1/2 hours and at 4 hours, 0.017% at six hours, 0.023% at nine hours, 0.049% at 21 hours and up to 0.107% at 31 hours. From their studies of normal, premature and "diabetic" infants it was found that the blood sugar levels of the premature and diabetic groups were nearly the same and considerably higher in the normal group. The averages given were

as follows: normal - 0.0499%; premature 0.0318%; and "diabetic" 0.297%. In their conclusions they felt that the blood sugar level was significantly lower than that of the normal infant. In the above cases of hypoglycemia there was no response to administration of glucose, the same lack of response is reported by Randell and Rynearson.

It would appear from a review of the literature concerning blood sugar levels in the infant of a diabetic mother that findings are quite variable. It is obvious that additional work need be done before any definite conclusion can be reached.

It is of interest to note in reviewing the results of blood studies on these "diabetic" infants, that immature types of cells are frequently reported. Given, Douglas and Tolstoi found an abnormally high number of nucleated red blood cells in their smears. Miller, Hurwitz and Kuder observed 45,000 erythroblasts per cu. mm. of blood in one case. Miller and Ross report blood counts on one infant in which 15,900 and 6,720 normoblasts were counted on the fourth and sixth days respectively, and a normal blood count on the eleventh day. Another of their infants exhibited 880

nucleated red blood cells the first day and 4,600 per cu. mm. the second day. A count of 35 normoblasts per 100 white blood cells on the third day suggested that the infant had erythroblastosis fetalis. Of the six infants studied by Miller & Ross, two had findings suggestive of erythroblastosis fetalis. White also reports a syndrome not unlike that of erythroblastosis and occurring in Rh+ mothers. Sisson, as well as Given, Douglas and Tolstoi, observed one fatality each in which the findings were those of erythroblastosis.

It is apparent from these studies that some "diabetic" infants exhibit clinical findings which are similar to those of erythroblastosis fetalis. There seems to be no connection with the Rh blood factor, and as yet, the etiology has not been determined.

Morbidity

Many of the infants of diabetic mothers, including those delivered two to four weeks before term, have the appearance of having reached maturity. In spite of this appearance the clinical behavior of

such infants frequently resembles that seen in the premature infant. A considerable number are so premature in their clinical behavior that they fail to survive the neo-natal period. Other infants, while they manage to survive, have a stormy neo-natal period. The morbidity among "diabetic" infants is generally considered to be quite high. Some of the causes of this morbidity will be discussed.

One of the most common symptoms observed by White, Sisson and others, in these infants was respiratory difficulty. It was often seen that an infant, after birth, would cry normally and be slightly sluggish in attaining a normal color. In a short while, two to three hours, it would develop a slight respiratory grunt. This gradually became more accentuated and the respiratory rate would increase often to 100 - 110 per minute. Physical examination of these infants revealed a marked degree of atelectasis. White and Sisson both report atelectasis, shallow, rapid, incomplete breathing, cyanosis, and apnea to be a frequent finding. Twitching and muscular contractions of face and extremities often accompany the respiratory difficulty. Sisson

also noted that reflexes were suppressed. Palmer, Crampton and Barnes as well as Given, Douglas and Tolstoi, and others, confirm the findings of White and Sisson, respiratory difficulty with cyanosis was often encountered early in the neo-natal period.

Other complications found in the "diabetic" infant which contributed to the morbidity were poor activity, sluggishness, poor feeding, failure of the baby to maintain his normal temperature, aspiration of amniotic fluid and consequently pneumonia, and congenital anomalies.

After reviewing the literature it is apparent that the cause of the respiratory difficulty is yet to be determined. The factor of analgesics and anesthetics is pretty well ruled out because many deliveries have been accomplished under spinal anesthetic without pre-operative medication. In spite of this procedure respiratory difficulty was observed. Sisson suggests a possible intra uterine cause with involvement of the respiratory center. In other cases, however, he postulates the insufflation of amniotic sac contents as a precipitating cause. He concluded that cerebral anoxia with

involvement of the respiratory center appeared to be the cause of many of the symptoms presented by these infants. Gonce reports that atelectasis is produced by four factors: (1) maternal hydramnios (2) widespread edema (3) aspiration of amniotic fluid (4) faulty lung expansion due to CNS anoxia. White observed that atelectasis with respiratory difficulty may be explained on the basis of aspiration of amniotic sac contents and that proper care, i.e. aspiration of upper air passages, postural drainage, aspiration of stomach contents and O_2 administration reduces the morbidity in these infants. An early widely held theory was that of hypoglycemia. This does not appear to be tenable in view of more recent findings (Miller and Ross). Miller and Wilson in their series of 10 infants consider the possibility of the respiratory symptomatology being cardiac in origin. No conclusive evidence was presented, however they believe the theory warrants further attention. They state that in their 10 infants, atelectasis was notable by its absence in 21 roentgen examinations in the first 10 days of life. They observed that the symptoms

were almost entirely respiratory in character and that the cyanosis cleared in every instance when O_2 was administered. As evidence in favor of their theory they call attention to cases of so called "idiopathic cardiac hypertrophy" in a somewhat older group of infants, the outstanding symptoms of which are cyanosis, dyspnea, tachypnea and restlessness, similar to that seen in their 10 infants of diabetic mothers. Palmer, Crampton and Barnes feel that possibly the respiratory difficulty with cyanosis may be caused by cerebral edema. To combat this condition they intend to use magnesium sulphate orally to produce dehydration. No conclusive evidence was presented by these authors.

After a study of the size and weight of infants of diabetic mothers, it is reasonable to assume that delivery would be more difficult and the incidence of traumatic injuries would be greater. This is found to be true by numerous authors.

To further complicate matters, the incidence of breech delivery in these infants is greater than in normal infants. Both Joslin and White have reported breech presentation in 33% of their cases. It is

reported by White and others that uterine inertia and shoulder dystocia are common. Lavietes, Leary, Winkler and Peters state that large babies causing difficult deliveries with birth injuries occur with disturbing frequency in all reported series of pregnancy complicated by diabetes. Not only is delivery more difficult, but the duration of labor in primigravid diabetic patients is appreciably lengthened. Given, Douglas and Tolstoi report prolonged labor in 26% of primigravid diabetic patients. These authors found the evidence of breech presentation to be 9.9% or three times the clinic average. Their greatest difficulty in delivery of these infants was in delivery of the shoulders. As evidence for this statement they report four deaths in eight instances of shoulder dystocia, resulting from traumatic delivery. Traumatic injuries secondary to difficult delivery were variable in types and included fractured skull, clavicle or humerus, Erb's paralysis and facial paralysis. Apparently in shoulder impaction great traction is necessary which results in birth injuries. Zilliacus and Levietes, Leary, Winkler and Peters, also Frankel, found delivery to be difficult, in cases of large babies, due to shoulder dystocia.

Congenital anomalies are said to be more frequent among infants of diabetic mothers. White, in a study of 125 infants in 1943 observed that there were 26 defects in 22 infants. This observation revealed that one in six of these infants had a defect as compared with one in 55 for infants of normal mothers. Of greater importance, White noted that in these "diabetic" infants the defects were more gross and more deforming than those in normal infants. Three possible explanations for the congenital defects are advanced by White. First, on the basis of heredity, second, hormonal imbalance,and third, vitamin deficiency.

Higgins in 1935 produced similar defects in experimental animals by Vitamin B deficiency. There is evidence that congenital defects do occur among diabetics as well as their offspring. It is possible that any one or combination of the three may operate to produce congenital defects. Other investigators are not in complete agreement with White, Sisson, while he does not dispute the findings of White, found no significant incidence of associated congenital anomalies in his series. In one case, at post mortem, atresia of the pulmonary valve was

demonstrated. An identical finding was made by Miller, Hurwitz and Kuder in a study of 12 infants. Paton in a group of 38 infants found one congenital defect, namely cleft palate and hare lip. Harris and Fisichella report one congenital anomaly among eight infants, as does Bill and Posey. Skipper in 1933 reported congenital defects in 3% of 118 cases.

Mortality

As previously stated in this thesis, modern insulin therapy has decreased maternal mortality but has not reduced the high fetal mortality. While this thesis deals primarily with the newborn of a diabetic mother, the statistical data on mortality rates presented here will include, to some extent, the fetus.

Among the theories which have been put forth to explain the disturbances and high mortality rates of infants of diabetic mothers are:

(1) Inadequate regulation of the maternal diabetes

(2) The high rate of toxemia of pregnancy in the mothers

(3) Hormonal imbalance in the mothers

(4) Hypoglycemia in the infants

(5) Some hereditary factor similar to or linked with that of erythroblastosis fetalis.

Miller, Hurwitz and Kuder do not believe the increased death rate among fetuses and newborn infants is related primarily to the severity of the maternal diabetes. They cite as evidence of this theory the high mortality rate in the pre diabetic period before the development of symptoms in the mother.

White and her co-workers believe that both the toxemia in the mother and the abnormalities in the infant are due to an endocrine disturbance. Fetal death is associated with high concentration of gonadatrophic substances. When pregnant diabetic women under their care received appropriate endocrine therapy a reduction in toxemia of pregnancy and of neonatal mortality was observed. (Barnes & Morgans are not in agreement.) This theory is supported by Zilliacus, but not by the Smiths. Smith and Smith found fetal mortality in the presence of normal endocrine balance. Bromberg and Toaff do not agree with White, but postulate a disturbance in water

metabolism. They feel that vascular damage leading to impaired blood supply to the uterus and its contents seems to explain both recurrent toxemia and habitual fetal death.

Hypoglycemia, as previously discussed, is not a constant finding in these infants. The blood sugar levels of all newborn infants are relatively low during the first day of life, therefore does not seem to be a valid explanation for the difficulties observed.

Other causes of mortality that have been demonstrated in these infants are: congenital anomalies, traumatic injuries at birth and as a result of bouts of keto acidosis and premature delivery.

Congenital anomalies, discussed under morbidity, are a cause of mortality but this author does not believe it to be a major factor except in isolated cases.

Given, Douglas and Tolstoi are impressed that bouts of keto acidosis have a definite bearing on the viability of the infant. Seven of the twelve patients whose infants died and who had no evidence of toxemia of pregnancy had bouts of keto-acidosis and insulin

reactions during the ante-natal course. Three of these patients went into premature labor spontaneously and delivered premature infants which died.

It is believed by almost all investigators (not confirmed by Miller, Hurwitz and Kuder except in the very high weight range) that trauma incident to difficult delivery is a major cause of not only morbidity but nortality in these infants. Not only does size and weight complicate these deliveries but also the high incidence of abnormal presentation. According to Cox, 1950, on the fetal risk in breech delivery, the fetal mortality in breech delivery for uncomplicated causes with mature infants is 4.98% for 16 years and 3.21% for the last 5 years. He further found that fetal mortality is 10% for infants weighing over 7-1/2 lbs. There figures concern normal babies, not those of diabetic mothers. Add to these figures of Cox, the increased size and weight of the diabetic infant plus the increased incidence of breech deliveries and obviously the mortality rate will be significantly increased.

Randall reports a 96.2% survival of infants

delivered by caesarean section whereas a 62.5% survival rate was noted when vaginal delivery was the method of choice. Given, Douglas and Tolstoi consider impaction of the shoulders a major complication and recommend caesarean section for infants estimated to weigh more than 4500 grams. Paton makes a definite statement that, "the surest cause of death in the baby of the diabetic mother is the trauma incident to delivery of a large baby through an inadequate pelvis". Therefore, he believes the indication for Caesarean section should be liberal. Miller, Hurwitz and Kuder found no correlation between the birth weight of the infant and the mortality. They postulate the presence of a lethal factor for the fetus which may be in effect from 15 to 20 years before the onset of diabetes can be recognized, and one effect of this factor becomes greater as the mother approaches the onset of clinical signs and symptoms of the syndrome. (Confirmed by Rike and Fawcett)

Statistical Data

Mortality Rate in Pregnancy Complicated by Diabetes

Author	Date	Patients	Pregnancies	Fetal Mort. in %
Williams	1909	43	66	49
Joslin	pre insulin	-	108	44*
Joslin	1935	-	122	43
Skipper	1933	33	37	41
Potter & Adair	1936	15	16	41
Joslin, Root White & Marble	1939	-	245	38
Lawrence & Oakley	1942	44	54	37
Miller, Hurwitz & Kuder	1944	-	-	23.6
White & Hunt	1940	24	-	13
Sisson	1940	-	65	18
White	1943	125	-	12
White	1947	66	-	3 (Hormonal balance corrected)
White	1947	58	-	53 (Hormonal balance uncorrected)
Palmer, Crampton & Barnes	1948	39	-	23.1
Given, Douglas & Tolstoi	1950	28	-	21.4
Bill & Posey	1944	44	-	27
Paton	1948	38	-	26.3
Miller, Hurwitz & Kuder	1944	-	-	29.4
Rike & Fawcett	1948	55	-	16.6
Merchante	1949	26	-	15

* - 30% if therapeutic abortions were excluded.

The above statistics while they present some estimation of the mortality rate do not present an accurate picture. Some apparently are corrected so as not to include deaths prior to the time of

viability. Nevertheless it is obvious from these above figures that the mortality rate among infants of diabetic mothers is considerably higher than in the non-diabetic group. Some workers, as mentioned previously, were not in agreement with the theory of hormonal imbalance as proposed by White, however it would seem from the decrease in mortality rate, after the hormonal balance is corrected that it is very definitely a factor.

SUMMARY

The pre insulin era was characterized by infertility, and when pregnancy did occur, by high maternal and fetal mortality. Insulin therapy, by controlling the diabetic condition, was instrumental in decreasing the maternal mortality to an almost negligible figure. In spite of the use of insulin the fetal mortality, in contrast to the maternal mortality, has remained high. This presents a problem today because of increased incidence of pregnancy complicating diabetes. The average age of diabetic mothers is greater than that of the normal mothers, as a result complications are more frequent.

While signs and symptoms are variable, the infant of a diabetic mother presents a rather typical symptom complex. The infant is larger than the average, due to obesity and edema. Splanchnomegaly is a frequent finding. Hyperplasia of the islet tissue of the spleen occurs, as well as hematopoiesis of the liver and spleen. There is a disturbance in water balance as evidenced by edema, weight loss and diuresis. The infant is mature in appearance

but clinical behavior is that of a premature infant. Respiratory difficulty, inability to maintain his temperature, sluggishness, poor activity, muscular contractions and decreased reflexes are often observed. Jaundice is not uncommon.

The average weight of these infants exceeds that of the normal infant. The basis for this increase is not clearly understood and is of a controversial nature. Hyperglycemia in the mother is considered to be the cause by some, while hormonal imbalance has been the theory of others. Other writers have incriminated the hypophysis, postulating a growth promoting effect from the diabetogenic principle.

The findings of enlarged heart, liver, and spleen, and atelectasis are common in the infant of a diabetic mother. The cardiac findings have been demonstrated by roentgenology. Some cases of respiratory difficulty may be of cardiac origin. Enlargement of the liver and spleen, atelectasis and hyperplasia of islet tissue in the spleen, have been found at autopsy. Pancreas, thymus and adrenal has been observed but not as often as the

heart, liver and spleen. The brain has been found to be smaller than average. Intra-cranial hemorrhage and edema of the brain and hemorrhage due to asphyxia are reported. Blood sugar levels have been extensively determined and the findings are by no means constant. Some authors report hypoglycemia, others hyperglycemia and still others found it to be similar to that of the normal infant. Additional work is necessary before definite conclusions can be reached. Immature blood cells are commonly encountered in smears of the blood of these "diabetic" infants. Findings suggestive of erythroblastosis fetalis in Rh- mothers have been observed. The etiology of this condition has not been determined. The variation in the internal organs has been attributed to hormonal imbalance.

The morbidity of these infants is generally considered to be high. Some are so premature in their behavior that they fail to survive the neonatal period. Respiratory difficulty is common and is thought to be due to atelectasis or cardiac enlargement. The newborn is frequently sluggish, exhibits poor activity, feeds poorly and may fail

to maintain his normal temperature. Muscular contractions may occur and reflexes may be depressed. Dystocia as a result of abnormal presentations and the large size of the infant accounts for numerous traumatic injuries, which contributes to the morbidity. The incidence of congenital anomalies is higher in these infants.

The mortality rate is higher in infants of diabetic mothers than in normal infants. Poor control of maternal diabetes, toxemia, bouts of keto-acidosis, hormonal imbalance in the mother, hypoglycemia in the infants, hereditary factors and disturbed water balance have all been advanced as possible underlying causes for the increased mortality rate. More obvious causes of death are congenital anomalies, traumatic injuries during delivery and prematurity. After examining the data on mortality rates by various authors, it is apparent that the fetal mortality remains high, however it has been significantly reduced by the correction of hormonal imbalance. Whether this is definitely the answer to the problem of fetal abnormalities and mortality remains to be seen.

CONCLUSIONS

1. The maternal mortality rate has decreased following the use of insulin, but insulin therapy had little effect on the fetal mortality rate.

2. The infant of a diabetic mother is, on the average, of greater size and weight than the infant of a non-diabetic mother.

3. The increased weight in the infant of a diabetic mother is probably a result of hormonal imbalance, however, maternal hyperglycemia may be a factor.

4. Edema, obesity and splanchnomegaly in "diabetic" infants is not an uncommon finding.

5. Atelectasis, excessive hematopoiesis of the Islets of Langerhans, are frequently encountered at autopsy.

6. The blood sugar levels, as reported, are variable and inconsistent, therefore additional work is necessary before reaching any conclusion.

7. Infants of diabetic mothers exhibit an increased number of immature cells in the blood and often present a picture similar to that of erythroblastosis fetalis.

8. The morbidity rate among infants of diabetic mothers is considerably higher than seen in infants of non diabetic mothers.

9. The incidence of abnormal presentations and difficult delivery is increased.

10. Congenital anomalies occur more often in "diabetic" infants than in normal infants.

11. The mortality rate in infants of diabetic mothers remains comparatively high, and is quite possibly the result of maternal hormonal imbalance.

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