

the occurrence of attacks chiefly or solely during sleep or in the early mornings, the existence of a warning long enough to enable the patient to avoid heavy falls, and a satisfactory degree of control by medicinal treatment.

One further social problem is that of marriage. On the basis of the evidence about the heredity of epilepsy formerly noted, the chance of a child of an epileptic also becoming epileptic has been variously estimated as from 1 in 10 to 1 in 40 (Brain, 1926; Lennox, 1945b). The risk of transmission is probably much less still if attacks begin in adult life, or if the patient has no family history of epilepsy; also if attacks are the result of a definite brain injury. A family history in both partners greatly increases the risk. Electrical records of epileptic type in either partner or both partners have probably the same significance. The prospect of producing epileptic children is therefore far less than is generally believed, and this we can conscientiously explain to those concerned. The real risks in marriage are the anxieties and dangers caused in the home and at work by the attacks themselves: these known risks can be calculated and faced. Nevertheless, so great is the dread of epilepsy that many patients decline marriage or refuse to have children. Both decisions are probably wrong, but they are understandable.

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DIABETIC FERTILITY, MATERNAL MORTALITY, AND FOETAL LOSS RATE

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Fertility

Pregnancy in diabetic women in the pre-insulin era was a rare event. Skipper (1933) credits Bennewitz (1826) with the first recorded case. Amenorrhoea due to uncontrolled diabetes accounted for the low fertility rates of 2-6% quoted by Lecorché (1885), von Noorden (1909), and Skipper (1933). The diabetic control that followed the introduction of insulin in 1923 largely abolished the amenorrhoea and produced a concomitant increase in fertility.

Skipper (1933), reviewing the records of the London Hospital, noted a fertility rate of 15% amongst 177 diabetic women between 1923 and 1931, compared with a rate of 2% amongst 190 comparable diabetic women between 1893 and 1922, while Eastman (1946) observed a fertility rate of 28.6%.

The rate of diabetic to non-diabetic pregnancies admitted to large obstetric hospitals has shown a similar rise. Williams (1909) saw only one pregnant diabetic during his thirteen years in charge of the obstetric service at Johns Hopkins Hospital, and in his review of the literature found only 65 recorded cases, whereas Mengert and Laughlin (1939) quote a ratio of 1 in 276, Barns (1941) 1 in 930, and Eastman (1946) 1 in 282. There were 70 diabetic pregnancies among the 20,438 confinements at the Simpson Memorial Maternity Pavilion of the Royal Infirmary, Edinburgh, between 1943

*This work was carried out during the tenure of a Lund Research Fellowship of the Diabetic Association.

and 1947—a ratio of 1 in 292. Insulin has therefore raised the status of the pregnant diabetic from that of a medical curiosity to one for which adequate provision must be made in any maternity service.

Maternal Mortality

An immediate maternal mortality of between 25 and 30% in diabetic women was associated with pregnancy in the pre-insulin era (Duncan, 1882; Offergeld, 1908; Williams, 1909; and others). The last-named author noted an immediate mortality of 27%, with an additional 23% during the ensuing two years, due to diabetic coma in the majority of cases. The insulin era has been associated with a progressively declining maternal mortality. Reviews of the literature by Skipper (1933) and Kramer (1935) revealed immediate maternal mortalities of 9.3 and 3.4% respectively. A mortality rate of less than 2% was quoted by Lawrence and Oakley (1942). White (1946) reported the loss of only one mother in 271 diabetic pregnancies between 1936 and 1946. Several smaller series of cases reported by Kramer (1935), Brandstrup and Okkels (1938), Shir (1939), Mengert and Laughlin (1939), and others reveal no maternal loss. There was one maternal death among the 70 pregnancies in the 62 diabetic women confined at the Simpson Memorial Maternity Pavilion, Edinburgh, between 1942 and 1947. It is thus apparent that the introduction of insulin has made pregnancy relatively safe for diabetic women.

Foetal Loss

The beneficial effects on the mother from insulin treatment have not been shared by the foetus. Henley (1947), reviewing the literature, noted a foetal loss of 43% in 169 pregnancies during the pre-insulin era, compared with 37.6% in 924 pregnancies since the introduction of insulin. The foetal loss rate in his own series was 55%.

The published figures of the foetal loss rate show considerable disparity. Mengert and Laughlin (1939) and Miller, Hurwitz, and Kuder (1944), considering only the foetal deaths occurring late in pregnancy and the deaths of babies during the neonatal period, found the foetal loss rate to be 18.2 and 23.6% respectively. On the other hand the foetal loss rates reported by Ronsheim (1933), Herrick and Tillman (1938), Barns (1941), and Lawrence and Oakley (1942), covering the whole course of pregnancy and the neonatal period, were 64, 43, 44, and 37% respectively.

Throughout this review of our cases the term "foetal loss rate" is taken to mean the percentage of all pregnancies not resulting in the birth of a baby living for at least 14 days. The term is therefore inclusive of all abortions, miscarriages, intrauterine deaths, stillbirths, and deaths occurring during the first 14 days of the neonatal period.

Using this definition, Table I shows that in spite of medical and obstetric supervision which we hope has been at least not inferior to the average in the country our foetal loss rate during the last five years has been as high as 51.4%.

TABLE I.—*Diabetic Foetal Loss Rate*

Period since Diagnosis of Diabetes	Total No. of Pregnancies	Foetal and Neonatal Loss	Foetal Loss Rate
0-2 years	35	19	54.3%
3 years and over	35	17	48.6%
Total	70	36	51.4%

In comparison with such figures recent results published by White (1946) are striking. This worker uses hormonal therapy to correct abnormal gonadotrophin and pregnanediol levels. She reports foetal loss rates based on

whether these levels are normal or abnormal and on whether patients have been given hormonal treatment of sufficient intensity to correct any abnormality which may exist. She found a foetal loss rate of only 3% when hormonal levels were normal, in comparison with 48% in cases with abnormal levels; but correction of abnormal levels by appropriate therapy resulted in a fall of the foetal loss rate to 10%. Her series, however, does not include abortions before the 24th week of pregnancy, so that her figures are not strictly comparable with our own. Even taking this into account, however, the foetal mortality reported by White is incomparably lower than in any other large series of cases—a result which may well be due to the correction of abnormal hormonal levels in her patients.

Pre-diabetic Foetal Loss: Historical Review

Throughout this article the terms "pre-diabetic" and "diabetic" refer respectively to the phases before and after the diagnosis of diabetes.

Allen (1939) first drew attention to the abnormally high rate of foetal loss occurring in the pre-diabetic period. Mengert and Laughlin (1939) have reported a foetal loss rate of 29.8% in 84 pregnancies during this period. Diabetes developed before the menopause in all their patients. Miller, Hurwitz, and Kuder (1944) have analysed 252 pre-diabetic pregnancies occurring in women developing diabetes during the child-bearing period. Their figures, which are exclusive of abortions and miscarriages, and which therefore include only stillbirths, intrauterine deaths, and neonatal deaths, show a foetal loss of 19.8% during the 20-year pre-diabetic period in comparison with a non-diabetic control rate of 5.4%. The maximum foetal loss rate of 35.4% occurred during the five years immediately before the diagnosis of diabetes and was considerably higher than the foetal loss rate of 23.6% which occurred in the 93 pregnancies among the same group of women after the onset of diabetes. Miller (1945), analysing the obstetric histories of 57 women in whom diabetes was diagnosed after the age of 40, reported an overall pre-diabetic foetal loss of 8.3% rising to 15.8% in the 15 years immediately before the diagnosis of diabetes.

Henley (1947) found a loss of 18% in 160 pre-diabetic pregnancies. His survey covered the pre-diabetic phase of 46 women in whom the disease was diagnosed between the ages of 25 and 69. Dolger and Herzstein (1944) and Herzstein and Dolger (1946) have failed to substantiate these findings. The reports of these workers are based on the pre-diabetic histories of 200 married diabetic women, 94 of whom developed the disease before the age of 45. They conclude that, although there is a significant increase in the foetal loss rate during the five years immediately before the diagnosis of diabetes, yet for pre-diabetic periods of longer duration the rate is not significantly different from that of non-diabetic women. Miller (1946) has challenged this conclusion, and by applying the χ^2 test to their figures has shown the difference between the pre-diabetic foetal loss rate for the 15 years before the onset of diabetes and the control foetal loss rate to be statistically significant. The absence of a uniform definition of foetal loss rate throughout the literature makes precise comparisons of figures impossible.

We have also been impressed by the high rate of foetal loss characterizing the pre-diabetic histories of many of our patients. The present survey deals with the pre-diabetic histories of 165 women attending the diabetic out-patient department of the Royal Infirmary, Edinburgh. All patients were interviewed personally. The group was unselected, and represents 165 consecutive attendances of parous diabetic women at the department.

Present Investigation

Standard Rate of Foetal Loss.—The first step in this investigation consisted in establishing the foetal loss rate in a comparable group of non-diabetic women. This presented many difficulties. The report of the Registrar-General for Scotland is exclusive of abortions and therefore does not give figures of "total" foetal loss according to our definition. Equally unsatisfactory were the histories of patients admitted to local maternity hospitals, since the admission to such institutions is often limited to primiparous patients and to those developing complications of pregnancy. Our diabetic patients are drawn in almost equal proportions from urban and rural districts. Records from the city clinics were consequently not entirely comparable. The standard rate of foetal loss finally chosen for comparison was that of the non-diabetic women attending the Ayr County Maternity Service. This service caters for all pregnancies, normal and abnormal. Further, the patients are drawn from urban centres such as Kilmarnock and from the wide rural districts of Ayr County. Obstetric histories of 1,027 women admitted to the above service in 1942 were analysed. Among the 3,276 pregnancies involved there was a foetal loss of 263 (8%). The components of the foetal loss rate were as follows: abortions and miscarriages, 2.8%; stillbirths, 3.2%; deaths occurring in the first 14 days of the neonatal period, 2%.

Variables Affecting the Foetal Loss Rate.—In the case of non-diabetic women the foetal loss rate might be expected to vary with such factors as the social class and physical condition of the mother, the age of the mother at the time of pregnancy, and the number of previous pregnancies. In a strict analysis it would have been necessary to investigate the foetal loss rate corresponding to each of these variables and to each combination of variables. Such subdivision was, however, impracticable: apart from the difficulty of establishing definitions of social class and physical condition, the numbers involved when such subdivision was undertaken were too small to make statistical conclusions valid. It was assumed, therefore, that these variable factors were "randomized" in our data, and that they were homogeneous when any two rates of foetal loss were compared. The comparisons made above indicate that the foetal loss rate of 8% among non-diabetic women can be used as a satisfactory standard for comparison with the foetal loss rates of the diabetic women concerned in the present survey.

Results

The 165 patients involved were divided into two main groups: (1) insulin group—132 women in whom the administration of insulin was necessary for diabetic control; (2) non-insulin group—33 patients in whom dietary treatment alone was sufficient for diabetic control. Each group was subdivided into: (a) young diabetics—women in whom diabetes was diagnosed before the age of 45; and (b) old diabetics—women in whom diabetes was diagnosed after the age of 45.

TABLE II.—*Insulin Group—132 Insulin Patients*

Pre-diabetic Period	Total No. of Pregnancies	Foetal and Neonatal Loss	Foetal Loss Rate
0-2 years	20	10	50.0%
3-9 "	58	12	20.7%
10-19 "	129	21	16.3%
20+ "	252	29	11.5%
Total	459	72	15.7%

Insulin Group

Table II shows the pre-diabetic foetal loss rate in the 132 patients who were taking insulin. It will be noted that the overall foetal loss rate of 15.7% is similar to the 18% quoted by Henley and is twice the non-diabetic control rate of 8%. On the whole there is a progressive increase in the foetal loss rate as the time when diabetes was first diagnosed is approached. The foetal loss rate of 11.5% for pre-diabetic periods in excess of 20 years steadily reaches a maximum in

the two years immediately before the diagnosis of diabetes. The foetal loss rate of 50% for the two-year pre-diabetic period in the present survey manifestly represents figures for young diabetics only, the last pregnancy among the old diabetics having occurred not less than four years before the diagnosis of diabetes.

TABLE III.—*Young Diabetics—59 Insulin Cases. Foetal Loss Rate According to Pre-diabetic Period*

Pre-diabetic Period	Total No. of Pregnancies	Foetal and Neonatal Loss	Foetal Loss Rate
0-2 years	20	10	50.0%
3-9 "	49	10	20.4%
10-19 "	45	9	20.0%
20+ "	10	1	10.0%
Total	124	30	24.2%

Young Diabetics.—Table III shows the pre-diabetic foetal loss rate among 59 young diabetics requiring insulin. It will be noted that the overall foetal loss rate of 24.2% in this group is three times the non-diabetic control rate of 8%—a ratio similar to that observed by Miller, Hurwitz, and Kurden (1944). Their foetal loss rate of 35.4% in the 1-5-year pre-diabetic period is comparable to the 50% during the 0-2-year period in our series, since we found the foetal loss rate of 50% in the 0-2-year phase to be substantially higher than that occurring in the 3-5-year period. We believe that the high foetal loss rate of the immediate pre-diabetic period is the characteristic feature of the pre-diabetic state, to be discussed later.

TABLE IV.—*Old Diabetics—73 Insulin Cases. Foetal Loss Rate According to Pre-diabetic Period*

Pre-diabetic Period	Total No. of Pregnancies	Foetal and Neonatal Loss	Foetal Loss Rate
3-9 years	9	2	22.2%
10-19 "	84	12	14.3%
20+ "	242	28	11.6%
Total	335	42	12.5%

Old Diabetics.—Table IV shows the pre-diabetic foetal loss rate among 73 old diabetics requiring insulin. An overall loss of 42 (12.5%) occurred in 335 pregnancies. As none of these women had been pregnant for at least four years before the onset of their diabetes, and usually for a much longer time, it is not surprising that they fail to show the very high foetal loss rate characterizing the immediate pre-diabetic phase of the young group of women. Miller (1945) reports similar observations.

TABLE V.—*Comparison of Foetal Loss Rate in Insulin and Non-insulin Cases*

	Insulin			Non-insulin		
	No. of Patients	No. of Pregnancies	Foetal Loss Rate	No. of Patients	No. of Pregnancies	Foetal Loss Rate
Young diabetics	59	124	24.2%	6	30	26.7%
Old " "	73	335	12.5%	27	115	11.3%
Total	132	459	15.7%	33	145	14.5%

Non-insulin Group

The patients requiring only dietary treatment for the control of their diabetes form a small group of 6 young diabetics and 27 old diabetics (Table V). The overall foetal loss rate of 14.5% in this group is not significantly different from the rate of 15.7% in women requiring insulin. Subdivision of the non-insulin group into old and young diabetics revealed foetal loss rates not significantly different from those observed in the insulin group. The similarity in pre-diabetic foetal loss rates of patients requiring insulin and those controlled by dietary treatment alone has been commented on by Herzstein and Dolger (1946). There seems, therefore, to be no relation between the severity of the ensuing diabetes and the pre-diabetic foetal loss rate.

All comparisons of the foetal loss rates between the various groups and the control group discussed above have been subject to the χ^2 test and have been found to be statistically significant.

Discussion

Our observation of an abnormally high foetal loss rate for pre-diabetic periods of up to 20 years confirms the findings of Miller, Hurwitz, and Kuder (1944) and Miller (1945). Our observation of a maximum foetal loss rate among young diabetics in the years immediately before the diagnosis of diabetes still further confirms the findings of these workers.

The similarity of the foetal loss rate in the immediate pre-diabetic phase and in the post-diabetic period raises a doubt whether the immediate pre-diabetic period is in fact pre-diabetic. Herzstein and Dolger (1946) point out that the 0-5-year period is not wholly pre-diabetic, as it may include an unspecified number of undiagnosed diabetics, since it is never easy to determine the exact date of onset of diabetes. We cannot entirely accept this view, for the following reasons: first, in the majority of young diabetics the disease comes on acutely, leaving little doubt about its approximate date of onset; secondly, the features of diabetes, such as glycosuria, polyuria, loss of weight, etc., tend to be aggravated by pregnancy, and it therefore seems unlikely that had clinical diabetes been present during the 0-2-year period it would have been completely overlooked by the obstetrician in the majority of cases; lastly, and most important, Table III shows a significant increase in the foetal loss rate for at least a decade before the diagnosis of diabetes was made, and it is impossible to believe that these young patients were suffering from undiagnosed diabetes for as long as five years.

It seems, therefore, that there is a factor conducive to foetal mortality which may be active for as long as 20 years before the diagnosis of diabetes and very active for the immediately preceding five years. The precise nature of this factor still remains uncertain. It is probable that the factors responsible for the large babies, the high foetal loss rate, and the ensuing maternal diabetes have a common basis in some general metabolic disturbance in the mother, and that the features of clinical diabetes, such as polyuria, glycosuria, thirst, etc., are a very late stage of this metabolic disturbance, an early feature of which is a high foetal loss rate.

Summary

Insulin therapy has increased the fertility of diabetic women and has made pregnancy a relatively safe proceeding for the mother, but has failed to produce a very significant decrease in the foetal mortality rate in diabetic women.

The pre-diabetic obstetric histories of 165 women in whom diabetes was diagnosed between the ages of 25 and 69 have been analysed. The overall pre-diabetic foetal loss rate was twice the non-diabetic control rate.

In those patients in whom diabetes was diagnosed before the age of 45 the pre-diabetic foetal loss rate was three times the non-diabetic control rate. The maximum pre-diabetic foetal loss rate, which was six times the control rate, occurred in the two years immediately before the diagnosis of diabetes was made and was as high as that observed after the onset of clinical diabetes.

In those patients in whom diabetes was diagnosed after the age of 45 the pre-diabetic foetal loss rate, which in this group was one and a half times the non-diabetic control rate, failed to show the dramatic rise immediately before the diagnosis of diabetes observed in the younger group of women.

There appeared to be no relation between the severity of the ensuing diabetes and the pre-diabetic foetal loss rate.

The onset of clinical diabetes may be a late stage in some general metabolic disturbance an early feature of which is a high foetal loss rate.

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PREGNANCY COMPLICATED BY DIABETES MELLITUS

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During the past twenty years 45 patients with definite diabetes mellitus have been observed in 58 pregnancies at University College Hospital. The incidence was 1 in 580 deliveries. This high figure is due to the fact that a number of the patients were referred to the Obstetric Unit from the Diabetic Clinic of the hospital. Pregnancy in the diabetic is an infrequent occurrence, and is in part due to the decreased fertility of the diabetic patient and in part to the fact that diabetes is much commoner in women during the latter portion of the child-bearing period, when pregnancy is less frequent (Barns, 1941).

In 48 of the pregnancies diabetes had been diagnosed and treated by a physician before the onset of the pregnancy. In the remaining 10 pregnancies the diagnosis was made during the pregnancy on the strength of a fasting blood sugar of 130 mg. per 100 ml. or over, a typical blood-sugar curve, and history of diabetic symptoms. The diagnosis was subsequently confirmed after the pregnancy. Hence in approximately one-quarter of the patients pregnancy appeared to unmask the condition of diabetes by precipitating the onset of symptoms or actually to initiate the clinical onset of the disease, which persisted, although usually in a milder form, after the pregnancy in question.

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