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PROGNOSIS IN DIABETIC PREGNANCY

BY

WILFRID OAKLEY, M.D., F.R.C.P.

Physician, King's College Hospital

The observations in this communication are based on two series of diabetic pregnancies: (1) 275 pregnancies supervised and delivered at King's College Hospital, referred to as the K.C.H. series; and (2) 458 pregnancies, details of which were collected from different centres in Great Britain, and referred to as the Q series. A detailed analysis of some of this clinical material has already been published (Peel and Oakley, 1949).

I will first deal briefly with the maternal aspect and then pass on to the more controversial and less satisfactory problem of the fate of the foetus.

The Maternal Aspect

In the Q series of 458 pregnancies 13 mothers died—in eight the cause of death was diabetic coma, and three of these died undelivered. Of the remaining five deaths two were due to peritonitis and one each to pneumonia, pulmonary embolism, and eclampsia, giving a maternal mortality rate of 2.8%. In the K.C.H. series of 275 pregnancies there were four deaths due to pulmonary embolism, septicaemia, cholaemia, and massive collapse of the lung; there were no deaths in diabetic coma and none of the patients died undelivered—giving a mortality rate of 1.4%. These figures show that death attributable to diabetes still does occur, but it can always be prevented by proper supervision of the mother.

In this connexion the insulin requirement in at least 75% of cases rises during the second and third trimesters, and —what is perhaps more important—the renal threshold in about the same percentage falls at about the fourth or fifth month of pregnancy. This constitutes one of the chief difficulties from the point of view of control of the maternal diabetes, and is usually first recognized by the development of heavy glycosuria and often severe ketosis in a previously well-balanced diabetic. To overcome this it is advisable to raise the carbohydrate content of the diet to 200 g. and give the mother a morning injection of soluble insulin and a second injection before tea of soluble insulin mixed with enough P.Z.I. to render the morning urine free of acetone bodies. If ketosis persists the addition of about 20 g. of glucose to each of the four meals usually clears it up. It is now well known that the maternal mortality rate can in this way be kept to a very low figure, but less is known about maternal morbidity of diabetics following pregnancy. The following points were therefore investigated: (1) insulin requirement following pregnancy; and (2) incidence and aggravation of diabetic complications: (*a*) retinitis, (*b*) hypertension, and (*c*) albuminuria. In none of the last 80 pregnancies of the K.C.H. series was there any significant increase in insulin requirement following pregnancy and attributable to it.

As regards retinitis, four cases were of interest—two were patients of Dr. Lawrence's and two of mine. Both of Dr. Lawrence's cases developed severe retinal haemorrhages, mostly of the flame or linear variety, and in one case these were associated with oedema of the optic disks; in both, the retinal lesions disappeared after the pregnancy. In my cases—both long-standing diabetics of 21 and 13 years' duration—there were previous ocular complications; in the former severe bilateral diabetic cataracts which made it difficult to exclude the presence of early retinitis, and in the latter typical early retinitis. During pregnancy the former developed definite aneurysms, blob haemorrhages, and patches of early exudate, and these have since progressed to retinitis proliferans with severe loss of vision. In the other case the retinitis has progressed since pregnancy. In both cases there has been an increase in albuminuria and a rise in blood pressure. These two cases are mentioned in detail because, from the maternal point of view, they are of great importance in connexion with the decision whether or not, in long-standing diabetics, pregnancy should be advised or be allowed to proceed. In the remaining 10 cases with retinitis at the onset of pregnancy there has been no appreciable change or evidence of deterioration, although two of them have been through two pregnancies. It is possible, therefore, that the progression of the retinal complication in the two cases would have occurred quite apart from the pregnancy, as, in fact, it very often does in such long-standing cases.

The question of hypertension and albuminuria is considered in connexion with toxaemia of pregnancy.

Toxaemia of Pregnancy

It is generally recognized that toxaemia is a relatively frequent complication of diabetic pregnancy. It is referred to again in connexion with foetal mortality, but I thought it would be worth while trying to follow up the toxaemic cases with a view to finding out whether they showed an unexpectedly high incidence or rapid development of hypertension and albuminuria following pregnancy. Interpretation of results is made difficult by the small number of cases and the fact that diabetics are apt to develop hypertension and albuminuria quite apart from pregnancy; some help, however, is to be gained from the relatively young age of the patients studied and the recognized association between these complications and the duration of the diabetes.

Of the last 222 diabetic pregnancies at King's College Hospital, 24 have been complicated by toxaemia, which on two occasions has occurred with successive pregnancies in the same patient. Three of the 24 cases are untraced, one died with eclamptic fits and cholaemia a few hours after delivery of a normal child which survived, and one had uraemia due to chronic nephritis. The remaining 19 cases have been followed with special reference to hypertension, albuminuria, and retinitis. In 13 there is no evidence of change in any of these respects following the toxaemic pregnancy, the only instance of hypertension being in a woman who had a benign essential hypertension before the pregnancy,

TABLE I.—*Late Effects of Toxaemia of Pregnancy*

Case No.	Before Toxaemia				After Toxaemia			
	B.P.	Alb.	Retinitis	Interval	B.P.	Alb.	Retinitis	Duration of M.D.
1	Normal	0	0	4 yrs.	132/98	0	0	12 yrs.
2	130/90	Sl. trace	?	7 ,,	120/90	0	Severe	11 ,,
3	148/80	0	0	4 ,,	170/90	0	0	11 ,,
4	130/80	Trace	0	1½ ,,	160/90	Sl. trace	0	23 ,,
*5	130/90	,,	0	¾ yr.	130/80	++	Early mild	16 ,,
*6	130/80	0	0	4 yrs.	160/100	0	0	10 ,,
				8 ,,	195/110	0	0	14 ,,

* Two toxaemic pregnancies.

which was no worse after it. The remaining six cases are summarized in Table I. It will be noted that both patients who had two toxaemic pregnancies are included in this small series. It is also interesting that in all six cases the diabetes had been present for 10 or more years; but this makes the interpretation of results more difficult, as diabetes of this duration may, quite apart from pregnancy, be associated with some hypertension, albuminuria, and retinitis. In these circumstances, it would be quite wrong to conclude that toxaemia of pregnancy constitutes a graver danger to the diabetic than to the non-diabetic mother, and I think the same can probably be said regarding the child.

Fate of the Foetus

Let me now turn to the prognosis in diabetic pregnancy from the point of view of the child. That an abnormally high percentage of these pregnancies result in stillbirth or neonatal death cannot be denied, that many different theories have been put forward to account for this high foetal loss also cannot be denied, but the fact that we still know little or nothing of the cause of this loss, if not actually denied, is being obscured, in my opinion, by the unwarranted acceptance of unproved theories and uncontrolled experiments. The results of the two series of pregnancies—733 cases in all—are applied to some of the theories put forward to account for this high foetal mortality rate in order to show that none of these theories will stand up to a critical analysis of a sufficiently large series of diabetic pregnancies.

(1) Control of the Maternal Diabetes

In 1942 Lawrence and Oakley recorded 54 diabetic pregnancies and showed that, if these were divided into three groups according to the degree of control of the maternal diabetes, the foetal mortality rate in the worst group was

TABLE II.—*Relation of Foetal Mortality to Age of Onset of Maternal Diabetes*

Age of Onset of Diabetes	No of Babies	Foetal Mortality
1–15	70	21 (30%)
16–24	105	24 (23%)
25 and over	92	29 (31%)

70% and in the best 23%, the intermediate group being 50%. These results suggest that poor control will raise the foetal loss rate, but also that good control will not lower it below the high figure of 23%.

(2) Severity of Maternal Diabetes

Gilbert and Dunlop (1949) have shown that there is no significant difference between the foetal mortality rate in non-insulin-treated and insulin-treated diabetic mothers; this finding has been confirmed by other workers and by me.

(3) Age of Onset of Maternal Diabetes

The relationship between the age of onset of the maternal diabetes and the foetal mortality from maceration, stillbirth, and neonatal death has been studied by Forgen Pederson (1949). In a series of 147 babies he found that when the onset of maternal diabetes was during the ages of 1 and 15 the foetal mortality rate was 42%, during 16 and 24 years 29%, and over 25 years 6%. He therefore concluded that when diabetes begins in childhood the foetal mortality rate is high; when the patient is grown-up before the onset of her diabetes the foetal mortality is far less. In order to test the validity of this statement the mortality rate in a series of 267 babies delivered of diabetic mothers at King's College Hospital was related to the age on onset of the maternal diabetes (Table II); the results obtained fail to confirm the existence of any direct relationship.

(4) Duration of Maternal Diabetes

It has also been suggested that the duration of the maternal diabetes may be a factor in the production of the high foetal mortality rate. A series of 665 pregnancies was therefore analysed from this point of view (Table III). These

TABLE III.—*Relation of Foetal Mortality to Duration of Maternal Diabetes*

Duration	Q Series				K.C.H. Series			
	Cases	S.	N.	Total	Cases	S.	N.	Total
0–4 yrs.	209	66	18	84 (40·2%)	97	19	10	29 (30%)
5–9 ,,	109	35	10	45 (41%)	72	9	11	20 (28%)
10–14 ,,	60	15	9	24 (40%)	55	4	10	14 (25%)
15–19 ,,	19	9	1	10 (52·6%)	28	4	2	6 (21%)
20+ ,,	5	2	0	2 (40%)	11	0	3	3 (27%)
Total	402	127	38	165 (41%)	263	36	36	72 (27%)

S. = Stillbirths. N. = Neonatal deaths.

figures show: the high foetal loss rate for all durations, the absence of any relationship between duration and foetal mortality, and the significantly lower mortality in the K.C.H. series, to which reference is made later.

(5) Diabetic Complications

As foetal loss could not be accounted for in terms of control, severity, or duration, it was decided to see whether the presence of retinitis or albuminuria in the mother before the onset of pregnancy could be a causal factor. Hypertension was not seriously considered, as it is almost always an indication for advising against pregnancy or, alternatively, for termination.

In spite of the relatively large number of pregnancies, these complications were found in comparatively few; 12 mothers had retinitis at the time of conception. In these 12 cases 14 pregnancies resulted in 12 live children and 2 neonatal deaths, a loss comparable to the uncomplicated pregnancies. Albuminuria, especially when associated with hypertension, is so well recognized as being associated with high foetal loss rate, even in non-diabetics, that it is not surprising that only six patients had persistent appreciable albuminuria at the time of conception and were allowed to continue; all six cases gave birth to live babies, and all survived and did well.

(6) Complications of Toxaemia of Pregnancy

Much stress has been laid on the frequency of toxaemia in these cases and upon the danger of this condition to the child. Table IV shows the results of toxaemic pregnancies in the K.C.H. and Q series. It will be seen that the toxaemic cases had a slightly higher foetal mortality rate

TABLE IV.—*Relation of Foetal Loss to Toxaemia of Pregnancy*

	Cases	Toxaemia					Total Foetal Loss
		No.	%	Live	Dead	Foetal Loss	
Q series	455	86	19·0	48	38	44·2%	40·3%
K.C.H.	274	31	11·3	21	10	32·2%	26·7%

than the others; but toxaemia is clearly not the answer, nor can one expect that any form of therapy directed against it will appreciably lower the foetal death rate.

Smith and Smith (1938) put forward the view that toxaemia of pregnancy is related to a disturbance of hormone balance and, pursuing the same line of thought, Priscilla White (1947) claims to have greatly lowered the foetal mortality rate by giving stilboestrol in increasing doses together with a daily injection of progesterone. In order to test the validity of this claim the Medical Research Council in England has organized an investigation in which a series of pregnant diabetics—selected at random—have received hormone therapy from an early stage of pregnancy, the controls being given inert tablets of identical appearance. The only ways in which treatment differed from that advocated by Priscilla White were that progesterone has been given by mouth in the form of ethisterone—daily injections being impracticable in the conditions existing in England—and the patients have not been admitted to hospital as a routine measure at least two weeks before delivery. Neither the physicians nor the obstetricians in charge know which cases have received active and which inert therapy, and it is hoped that, in this way, results of statistical significance will be obtained. Unfortunately, the results of this investigation are not yet available, but in a series of 50 pregnancies in which hormone therapy was given at King's College Hospital, 21 resulted in stillbirth or neonatal death, giving a foetal mortality of 42%.

(7) Mode and Time of Delivery

It has been shown in Table III that the foetal loss rate in the K.C.H. series was very significantly lower than that in the Q series; there are several possible causes for this. Where large numbers of cases are treated greater experience is apt to produce better results; close co-operation between diabetic and obstetric departments is also of great importance, as is regular diabetic and antenatal supervision. The main cause of the difference, however, is to be found in the time and mode of delivery.

TABLE V.—*Relation of Foetal Loss to Mode of Delivery*

Mode of Delivery	Q Series					K.C.H. Series				
	Cases	Live	S.	N.	% Loss	Cases	Live	S.	N.	% Loss
Spontaneous labour ..	129	83	23	23	35·6	17	14	2	1	18·0
Induced labour	126	91	23	12	27·8	36	23	9	4	36·0
Caesarean section ..	115	97	3	15	15·7	156	127	1	28	18·5
Total ..	370	271	49	50	27	209	164	12	33	21·5

S.=Stillbirths. N.=Neonatal deaths.

Table V shows the high loss rate associated with spontaneous labour in the Q series, the much lower figure in the K.C.H. series being due to the fact that all the cases so delivered went into labour spontaneously at or before the thirty-sixth week, at which time they would otherwise have been induced or had caesarean section. The figures for induction are high but comparable—primiparae giving a higher foetal death rate than multiparae, as might be expected. The figures for caesarean section are much lower, and again are comparable. It would appear, therefore, that in the Q series the large number of pregnancies allowed to continue to spontaneous labour accounted for the higher foetal mortality, and incidentally also for the fact that three mothers died undelivered. It will be seen from Table V that the practice in the K.C.H. series of terminating the pregnancy at about the thirty-sixth week by caesarean section or, in the case of those who have had a previous normal delivery, by induction has resulted in a great reduction in stillbirths but a considerable neonatal mortality. Until some reliable method of preventing death *in utero* in the last few weeks of pregnancy has been discovered—and I am not convinced that such a method yet exists—I feel that we are most likely to reduce the loss rate by obtaining a live baby and directing our efforts to prevent it from dying. This brings me to my last consideration—namely, the newborn baby.

The Newborn Baby.—The majority of neonatal deaths occur within 48 hours of delivery and are due to what appears to be respiratory failure; the baby has recurrent attacks of apnoea with cyanosis, in one of which it dies. Other possible causes of death are foetal hypoglycaemia and congenital deformities. The latter are relatively common, and 19 instances were observed in 221 consecutive diabetic pregnancies at King's College Hospital, giving an incidence of 8.6%. Such deformities could not be related to duration or control of maternal diabetes, and, although all the mothers were receiving insulin, there was no evidence that hypoglycaemia was more frequent or more severe than in those pregnancies which resulted in normal children.

(8) Foetal Hypoglycaemia

Although once regarded as a likely cause of neonatal death, there has recently been a tendency to discount this possibility. In order to arrive at a more definite conclusion it was decided to estimate blood sugars at two-hourly intervals on a series of babies, half of whom received no glucose and the other half 50% glucose hourly by mouth. In all, 17 babies received glucose and 18 no glucose, the respective neonatal deaths being two in the former and four in the latter series. The number of cases is too small to allow of any definite conclusions, but certain findings are of interest. In one of those that received glucose and died there was no demonstrable sugar in the blood one hour before death, while in the other the blood sugar at the time of death was 175 mg. per 100 ml. In the same series eight of those that lived had blood sugars of 30 mg. or less in the first six hours, and in four of these the level fell to 20 mg. or less; one survivor had no demonstrable blood sugar at two hours after delivery. Of the 18 babies that received no glucose, three of the four that died showed levels of 35 mg. or less per 100 ml. within six hours of death, and the remaining one had a blood sugar of 78 mg. four hours before it died. The blood sugars of six of those that lived fell below 35 mg. per 100 ml., and in four of these it was less than 20 mg. It is difficult, therefore, to say more than that death may occur with a normal blood sugar and survival with a very low one or even without any demonstrable sugar in the blood. This problem clearly needs further study.

Conclusion

Great emphasis must be laid on the importance of the nursing and management of the newborn infant. The use of an isolette in which both oxygen content of the air and temperature can be controlled, and regular suction if there are any signs of respiratory embarrassment, may help to reduce neonatal mortality. The use of continuous low-pressure suction and some form of mechanical respirator are under consideration in our department, and electrolyte and hormone studies are being carried out on these babies in the hope that they may shed some light on the present obscure problem of the high foetal mortality in diabetic pregnancy.

I acknowledge my indebtedness to Mr. John Peel, who was not only responsible for the obstetric management of these cases but also played a large part in the collection and analysis of the questionary series. I am grateful to Dr. R. D. Lawrence for access to the records of his private patients.

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