

Fetal Mortality in Diabetic Pregnancies*

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The fetal mortality in pregnancies of diabetic women is still high, and there is some disagreement as to the best treatment. One of the points in dispute is the value of hormone therapy during pregnancy. White^{1, 2} has reported a fetal mortality which is among the lowest obtained so far. She ascribes this success to the administration of stilbestrol and progesterone during pregnancy, but this explanation is not generally accepted. As stated, for example, by Brandstrup and Okkels,³ it would be valuable to elucidate the role of the control of the diabetes and the maternal hyperglycemia. This applies not only to the infant mortality, but also to the size, weight, water content, etc., of the infants and their subsequent fate, particularly with regard to the incidence of diabetes.

As part of the investigations which are being carried out in Lying-in Department B, Rigshospitalet, on problems pertaining to diabetes and pregnancy, it was planned late in 1945 to study these factors by an intensive classical treatment of the diabetes and by conservative obstetrical management, carried out by a small number of doctors. In this paper the fetal mortality will be reported.

LONG-TERM AND SHORT-TERM TREATMENT

The material summarized in Table 1 comprises all deliveries by diabetics in Lying-in Department B during the eight-year period 1946-1953. The weight limit was fixed at 1 kg. There were 161 mothers who gave birth to 192 infants in 189 deliveries. There were three twin births and the highest number of deliveries by any patient was three.

The material is divided into two groups according to the stage of pregnancy at which the patient first ap-

plied to the clinic. This occurs at very different stages, since the Department receives all kinds of obstetrical complications without selection and many emergency cases. A few diabetics attend from the very first months of pregnancy, while others are not seen until they are in labor. The majority, however, are seen toward the end of pregnancy. All those who were seen at a minimum of 53 days before the calculated term were classified as having long-term treatment; those who were not seen until later were considered to have had short-term treatment.

Patients who, according to the time of their first application, were designated as long-term cases were transferred to the short-term category if they were in coma, precoma or in labor, or had been delivered when first seen. The short-term classification was also applied in cases of fetal death or delivery within eight days after the first application (Table 2).

The skew value of 53 days was obtained as follows. In a previous study⁴ of the infants' blood sugar, patients

TABLE 1
Summary of Material

	Long-term treatment	Short-term treatment	Totals
Mothers	73	102	161*
Deliveries	78	111	189
Babies	80	112	192

*14 patients are included in both the long-term and the short-term groups.

TABLE 2
Patients seen for the first time 53 days or more before the calculated term, but transferred to the short-term group

Cause of Transfer	Number of Infants	
	Total	With birth weight of 2.5 kg. or over
Coma or precoma, or in labor at first attendance	8	3
Delivery or death of infant within 8 days after first attendance	12	2
Totals	20	5

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who had been in the Department for a continuous period of at least 32 days prior to delivery were designated long-term patients. Since delivery takes place on the average three weeks before the calculated term, the first application has been a minimum of 53 days before the calculated term. The 53 days are maintained as a limit, but the need for 32 days' stay in the Department prior to delivery is not included in the definition here, since in that case the long-term patients would be selected, including too many patients without complications indicating interruption. In a study of the value of a therapeutic method, it is assumed that all patients of the treated group have received some treatment. Therefore, it was necessary to make the above exception. As evident from Table 2, most infants weighed less than 2.5 kg.

The criteria for long-term patients are highly unfavorable for the therapeutic results in this group. That is to say, all deaths among the infants whose mothers applied to the clinic a minimum of 53 days before their calculated term are allotted to the long-term group after only eight days' treatment of the mothers, whether they have been outpatients or inpatients. Of course, what is important is that on the average the long-term patients have been treated for a much longer time than the short-term patients, as is apparent from Table 3. All the long-term patients and 14 per cent of the short-term patients were seen for the first time 53 days or more before the calculated term, and 78 per cent of long-term and 10 per cent of short-term patients had had a continuous hospital stay of 30 days or longer immediately before delivery. Fourteen patients are included in both the long-term and the short-term groups.

ROUTINE EXAMINATIONS

All the patients were examined by ophthalmologists for diabetic retinopathy and cataract and by X ray for calcified arteries of the arms and legs. In addition, frequent examinations were made for urinary tract infec-

tions, and daily examinations were made for proteinuria and hypertension. No search for calcification of pelvic arteries could be made during pregnancy, and in fact only one case with this condition was known.

TREATMENT

All cases were treated in the same way, but for varying periods of time, as indicated. The aim was to keep the blood sugar as near the physiological level as possible, to prevent acidosis and insulin reactions, and to prevent and combat toxemia and edema. In brief, the treatment was as follows. The diet contained 1800 to 2000 calories, 80 to 90 gm. of protein, 175 to 200 gm. of carbohydrate, and about 80 gm. of fat. In addition, a supplement of vitamins, calcium, and iron was given.

In an effort to keep the blood sugar low, four daily blood sugar determinations were made on inpatients. The extent to which this aim was attained is exemplified by the fact that in the first 18 long-term mothers the pregnancy level of the blood sugar (average of the four daily determinations during the last continuous stay in hospital, average 52 days) ranged from 108 to 167 mg. per 100 cc., and the common average level was 133 mg. Adequate doses of insulin were used, preferably crystalline protamine insulin (NPH insulin) plus regular insulin administered simultaneously twice daily. The average daily dose of insulin for all inpatients was about 70 international units (for details see Pedersen⁴).

Restriction of table salt and fluid to combat toxemia and edema was frequently prescribed. Abdominal amniotomy was tried in two cases. No hormones, mercurial preparations, ammonium chloride, rutin, or similar substances were used.

The schedule for visits and control was as follows: during the first months ambulatory control about every three weeks, and from the beginning of the fifth month every week. About eight weeks before the calculated

TABLE 3

Days before calculated term (first attendance) or delivery (continuous stay)

Diabetic group	Number of Days										Totals
	0— 9	10— 19	20— 29	30— 39	40— 52	53— 59	60— 69	70— 79	80— 89	90+	
First attendance:											
Short-term	3	2	14	32	40	2	6	3	3	2	107*
Long-term	0	0	0	0	0	21	16	10	10	21	78
Continuous stay:											
Short-term	41	31	28	8	2	1	0	0	0	0	111
Long-term	7	4	7	21	21	12	3	1	1	1	78

*No data available in 4 cases.

term the patient was hospitalized for prophylactic purposes and remained in the Department until delivery, which was usually induced about three weeks before term. This applied to uncomplicated cases. Complications which did not yield at once to ambulatory measures called for immediate hospitalization. In the presence of complications, delivery sometimes had to be induced before the 38th week.

As seen from Table 3, only a few of the long-term patients had been controlled throughout the pregnancy. The remainder were seen for the first time at a number of different stages of the pregnancy, and the short-term cases arrived so late that they were only inpatients. Before coming to the clinic the patients had been controlled at various medical outpatient or inpatient departments in Copenhagen. During the past few years, many have come from the Steno Memorial Hospital and the Hvidøre Hospital (private hospitals for diabetics). Some come from provincial hospitals, others from general practitioners, and some had no control at all. Moreover, some patients had attended the outpatient antenatal clinic of Rigshospitalet before coming to us. It must be borne in mind that the material is unselected, all kinds of patients coming at all periods of pregnancy, many as emergency cases.

The obstetrical management was conservative, but was conducted in the same manner in long-term and in short-term cases. Nearly all deliveries were induced—by drugs and/or rupture of the membranes—about the 38th week. Only 16 cesarean sections were performed (8 per cent), whereas forceps deliveries were common. It is planned to give details of the obstetrical management in a later paper.

After suction of the hypopharynx, all the newborn babies were placed in incubators and given oxygen, warmth, and humidity routinely for the first 24 hours. During this period all the babies were fasted (cf. Pedersen⁵).

The ambulatory control of the long-term patients was performed by the author, who received the advice of the obstetricians when necessary. All inpatients were treated daily by me, and the obstetrical management was conducted by a small number of obstetricians under the supervision of Prof. Brandstrup. A pediatrician was called whenever needed.

CLINICAL FEATURES

From Table 4 it will be seen that the frequency of severe diabetes was 63 per cent, of diabetic retinitis 23 per cent, and of calcified arteries 5 per cent; 44 per cent of the patients were primiparas. On the whole, the long-term and short-term series do not exhibit differences sufficiently marked to account for the difference found in fetal mortality, especially for infants with a birth weight of 2.5 kg. or over. The incidence of toxemia (unclassified) was 30 per cent, which agrees with other series of unselected cases (Jones⁶). The frequency of hydramnion was 50 per cent (more than 1000 ml.) or 20 per cent (more than 1500 ml.) (Pedersen and Jørgensen⁷).

CLASSIFICATION

An entirely satisfactory classification of pregnant diabetics remains to be found. This is also Oakley's⁸ opinion. This is not only because we do not yet know all the causes of the high fetal mortality, but because

TABLE 4
Comparison of long-term and short-term series

	Onset of Diabetes										White's Classification				Congenital Malformations			Primiparas	Cesarean Section					
	Age 12 Years or Less		Age 21 Years or Less		Duration of Diabetes 15 Years or More		Diabetic Retinitis (and cataract)		Proliferative Retinitis	Calcification of Leg (or Pelvic) Arteries	Diabetic Nephropathy*	Groups†		Total	Major	NO.	NO.		%					
	NO.	%	NO.	%	NO.	%	NO.	%				NO.	%							NO.	%	NO.	%	NO.
Long-term	15	19	45	58	15	19	20	26	2	6	8	22	28	51	65	26	33	4	5	1	29	37	13	17
Short-term	28	25	73	66	22	20	23	21	1	4	4	24	22	69	62	35	32	9	8	5‡	54	49	3	3
Totals	43	23	118	62	37	20	43	23	3	10	5	46	24	120	63	61	32	13	7	6	83	44	16	8

*In most cases varying degrees of pyelonephritis.
 †The number of cases belonging to group E cannot be stated.
 ‡Four deaths, birth weight less than 2.5 kg.

treatment may mask the natural course of the disease.

Thus, in this series the fetal mortality is only slightly increased for primiparas (primiparas 32 per cent, multiparas 23 per cent). It increases with increasing duration of diabetes (0-9 years, 23 per cent; 10-19 years, 30 per cent; 20 years or over, 45 per cent; and in the presence of diabetic retinopathy, 42 per cent). There is, on the other hand, no correlation with the age of onset of the diabetes (1-15 years, 31 per cent; 16-24 years, 19 per cent; 25 years or over, 30 per cent, which was found to be marked in a previous study (Pedersen⁹). There was, moreover, no convincing correlation with calcified peripheral arteries or the severity of retinitis. However, a larger group with a high mortality may be set up. This group should, on the basis of the present study, include the following conditions: diabetic retinopathy, cataract, calcified arteries, vascular nephropathy, or diabetes of more than twenty years' standing.

It will be seen that this group does not differ essentially from groups D, E, and F in White's¹ classification. This classification suffers from the practical disadvantage that an accurate classification into groups E and F presupposes fairly extensive knowledge of vascular complications before the patients become pregnant. Group F, vascular nephritis, includes constant albuminuria before the pregnancy, but not pyelonephritis with varying pyuria and intermittent albuminuria (White¹⁰). In our series, the number of cases belonging to group E cannot be stated, and the numbers in group F will be a minimum. However, for the time being I shall use White's classification, omitting group E.

It is suggested that the mortality for infants weighing 2.5 kg. or more should always be reported. The reasons are, among others, that the indication for therapeutic interruption before this weight has been attained may be lacking in uniformity, that a number of clinics supervise the patients only during the latter part of pregnancy, and that differences in fetal mortality due to major congenital malformations will decrease.

RESULTS AND DISCUSSION

The results of the treatment are given in Table 5. The mortality in the total material, 26 per cent, corresponds to that reported, for example, by Jones⁶ and to Oakley's⁸ series (King's College Hospital, London). The total mortality in our maternity hospital in previous years (1926-1945) was 38 per cent. Thus there is a definite, though not a large, gain.

It will be seen that the mortality in the long-term cases is 11 and 9 per cent, but 36 and 25 per cent in the

TABLE 5
Fetal mortality in long-term and short-term cases

	No. of Babies	Birth weight 1 kg. or over		Birth weight 2.5 kg. or over	
		No.	%	No.	%
Long-term	80	9	11	70	9
Short-term	112	41	36	92	25
Totals	192	50	26	162	18

short-term cases, for birth weights of 1 and 2.5 kg. and over respectively. In either case the difference is statistically significant.

In Table 6 the material is classified according to White.¹ Groups A and F are small, and as stated above, the number in F are a minimum. In the total series there is no increase in mortality from group B to C, and it is noteworthy that in our long-term series the mortality for groups A, B, C, and D is 8 per cent, with no increase between groups B, C, and D. It would appear most practical to combine groups A, B, and C into one group and D and F into another. As is apparent from Table 7, the mortality now increases from groups A, B, and C to groups D and F for both long-term and short-term cases. The long-term series exhibits a lower mortality in both groups, and the result is not altered by paying attention only to birth weights of 2.5 kg. or over.

Tables 5 and 7 show that 20 infants (18 per cent) in the short-term series weighed less than 2.5 kg. and that 18 of them died. In the long-term series there were 10 infants (13 per cent) with birth weights of less than 2.5 kg., including two pairs of twins. Only 3 of these died.

It was previously shown (Table 4) that the long-term and short-term series are comparable. In our opinion, the prolonged treatment in the long-term series is without doubt the cause of the lower mortality. Indeed, it is not surprising that the result may be improved by intensive treatment and supervision carried out by a few doctors.

The mortality in the long-term series, 11 per cent (Table 5), corresponds to that reported by Reis¹¹ and by Pease.¹² Neither of these series, however, contained as many cases of severe diabetes as the present one. The mortality in the long-term series is also as low as in the series of White¹ and Nelson.¹³ Table 8 sets out some differences and similarities between the long-term series and the series of Nelson. The latter contained only a few more severe diabetics (72 per cent) than ours (65 per cent).

TABLE 6
Fetal mortality classified according to White¹⁰
(Class E omitted)

Diabetic Group	Group A Glucose- tolerance test dia- betes (no insulin).	Group B Diabetes: onset 20+ yr. Dura- tion 0-9 yr. No Vascular disease.	Group C Diabetes: onset 10-19 yr., dura- tion 10-19 yr. No Vas- cular disease.	Group D Diabetes: onset less than 10 yr., duration 20 yr. or more. Calcified arteries in legs. Diabetic retinopathy.	Group F* Vascular nephritis
Long-term: No. of infants	1	28	25	21	5
Fetal loss	0	2	3	1	3
Short-term: No. of infants	5	38	34	32	3
Fetal loss	0	17	6	17	1
All cases: No. of infants	6	66	59	53	8
Fetal loss	0	19(29%)	9(15%)	18(34%)	4(50%)

*Minimum figures (cf. text).

TABLE 7
Fetal mortality in relation to White's Classification
and birth weight

	White's Classification Groups (E not stated)						
	A+B+C			D+F			
	Fetal loss		No. of Babies	Fetal loss		No. of Babies	
No.	%	No.		%			
Birth weight 1 kg. or over:							
Long-term	54	5	9	21	26	4	15
Short-term	77	23	30	35	18	51	36
Birth weight 2.5 kg. or over:							
Long-term	50	4	8	13	20	2	10
Short-term	64	11	17	28	12	43	29

Our material shows that without sex endocrine therapy and without extensive use of cesarean section, it is possible to obtain results which are as good as those of White in groups A, B, C, and D. As regards groups A and B, this is also evident from Reis's¹¹ series. Our series is still too small to assess the mortality for group F, but this seems to be the only group in which the mortality will exceed 10 per cent.

We intend to continue in the same way without administration of hormones. When the series has become larger, we shall analyse the long-term and short-term groups to find out which mortality-increasing factors our treatment has diminished and which it has failed to affect.

TABLE 8
Comparison of this series with that of Nelson, Gillespie, and White^{13*}

	Fetal mor- tality	Severe diabetics. White's groups C+D+ E+F	Primi- paras	Cesarean section	Rutin, mercu- hydrin, ammoni- um chlor- ide	Hor- mone treat- ment
White's series	10%	72%	Nearly 50%	70%	+	+
This series (long-term)	11%	65%	37%	17%	None	None

*In both series the following conditions existed: close individual supervision and management by a few doctors; best possible chemical control of diabetes; restriction of salt (and fluid); early timing of delivery; suction, incubation, and fasting of infants.

SUMMARY

Lying-in Department B, Rigshospitalet, Copenhagen, is a large Department receiving, without any selection, patients with complications as well as many emergency cases.

During the years 1946-1953 a total of 189 diabetic pregnancies were observed and 192 babies were born (birth weight 1 kg. or over). The fetal mortality was 26 per cent.

This material is divided into two groups: long-term treated and short-term treated cases, according to the stage of pregnancy at which the patient was first seen. The long-term cases were treated for a much longer time during the latter part of pregnancy than the short-term cases. Both groups received the same treatment, conducted by the same few individuals, and consisting of intensive classical management of the diabetes by diet and ample insulin and conservative obstetrical management. Cesarean section was used in only 8 per cent of the cases. No hormones were administered. All the infants were fasted for 24 hours. The rate of severe diabetics (Groups C, D, E, and F according to White) was 64 per cent, of diabetic retinitis 23 per cent, of calcified arteries 5 per cent, and of primiparas 44 per cent—without any differences between the long-term and short-term series.

In 111 short-term pregnancies (112 babies) the fetal mortality was 36 per cent; in 78 long-term cases (80 babies), it was 11 per cent. In the long-term series the fetal mortality in the White groups A, B, C, D, and F was 0, 7, 12, 5, and 60 per cent, respectively.

In view of the results obtained in the long-term series, we have not felt inclined to try sex endocrine treatment, but shall continue to collect a larger series of long-term patients, especially in the White group F.

While awaiting a more perfect classification, the author suggests a classification according to White (omitting class E) supplemented by separate statements

on the fetal mortality for birth weights of 2.5 kg. and over.

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