Special Article

Pregnancy in the Diabetic

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SUMMARY

A study of 300 pregnancies in 156 Irish diabetics is presented. Thirty per cent of the pregnancies were fifth or later, and the mean maternal age was thirty years. The abortion rate was 11 per cent, and the loss of viable infants was 10 per cent. There was no maternal death.

Control of diabetes was strict, and this is reflected in the occurrence of hypoglycemic coma on twenty-one occasions. Diabetic ketosis occurred in twelve cases—all of whom were unbooked emergency admissions. The influence of these complications on fetal survival is contrasted.

Pre-eclamptic toxemia and hydramnios in the mother, and respiratory-distress syndrome in the infant contributed heavily to infant loss.

Of recent years the aim has been to deliver at thirty-eight weeks in uncomplicated cases—usually by the vaginal route. The cesarean section rate for the whole series was 22 per cent, and for primigravidae was 29 per cent. A plea is made for a more dynamic approach to vaginal delivery. DIABETES *15*:830-35, November, 1966.

Kyle[1] illustrated the steady reduction in fetal mortality in pregnancies of diabetics by comparing published figures for 1930-40 with those for 1950-60. In 742 cases (seven series) treated in the earlier years, the loss varied from 14 to 50 per cent, while in the later period, 1,487 cases (twelve series), the loss was 8 to 20 per cent. It is of interest that within the same decade fetal mortality varied widely at different centers. Such variation is to some extent explained by differences in case material. White[2] introduced a classification system based on factors such as—maternal age at onset of diabetes; duration of diabetes; presence or absence of angiopathy. Kyle[1] applied this classification to seven published series (1,845 cases) and found a progressive increase in fetal loss from class B (16 per cent) to class F (37 per cent). There were only eighty cases in class A, but the fetal loss was 22 per cent. This may indicate that in any given series, factors may be operative which are not allowed for in White's system, so that it is important to characterize case material from other points of view.

During the years 1950-65, the writer was responsible for the medical care of 156 women during 300 pregnancies—90 per cent of the deliveries were at the National Maternity Hospital; the remainder at the Coombe Lying-In Hospital. These hospitals provide a community service and, as such, in the words of Jones,[3] "We are obliged to accept emergency cases and miscellaneous drifters infrequently seen in specialised centres. This has a devastating effect on fetal loss statistics." The extent of this problem is well expressed in the preamble to the most recent annual report of the National Maternity Hospital—"During 1964 there were 5,160 babies born in the hospital. The policy of admitting any woman in labor or in need of care from any part of the country, irrespective of bed occupancy, results in a high concentration of abnormalities. Twenty-one per cent, i.e., 1,055 of these cases did not attend the hospital on any occasion before admission." Thus, a number of our diabetics are referred late in pregnancy, sometimes with established complications. Late referral influences perinatal mortality, vide Pedersen[4] and Hagbard.[5] A further difficulty is that many of our patients live a considerable distance from the hospital (up to 200 miles), so that frequent antenatal visits may impose a considerable hardship. Finally, although age at marriage in Ireland is relatively advanced, a high degree of multiparity is common. In this series, the mean maternal age was thirty years, and 30 per cent of the pregnancies were fifth or later.

Management: Our methods are to a large extent conventional, and may be summarized as follows:

(1) Antenatal supervision by physician and obstetrician at fortnightly intervals until the thirty-second week, and thereafter at weekly intervals.

(2) Use of a weighed diabetic diet, aimed at restricting weight gain to twenty-one pounds, but respecting the protein needs of the fetus. Ketonuria in association with excessive renal leak of glucose is corrected by increasing carbohydrate intake.

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(3) Strict control of diabetes is maintained. At each antenatal visit, a midmorning and midafternoon blood glucose is estimated; patients living near the hospital also have a fasting test. Fasting levels of 100 mg. and postprandial levels of 150 mg. are regarded as the permissible upper limits.

(4) Hormones are not used and diuretics are prescribed only for the treatment of water retention.

(5) Patients are admitted one to two weeks before the date planned for delivery, but the loss of diabetic control or the development of a complication leads to immediate admission.

(6) During the sixteen-year period, principles of management have changed in only one significant respect—timing of delivery. With increasing experience, the "moment of truth" has been postponed, and we now feel that patients should not be delivered until the end of the thirty-eighth week unless special indications exist.

(7) Vaginal delivery is attempted unless there are obstetrical indications for cesarean section.

(8) Specialized pediatric care is available from the moment of delivery.

RESULTS

There were 300 pregnancies (302 fetuses) in 156 women—no mother died. In six cases the fetus was already dead before the patient was referred to our care. There were thirty-three abortions (11 per cent). Thus, there were 261 viable pregnancies (263 fetuses) in the series. The perinatal loss was twenty-six (10 per cent) of which sixteen were neonatal (within seven days of birth). Table 1 shows the influence of grading (by White's classification) on fetal survival.

TABLE 1

Outcome related to classification of White

Class	Infants	Live
A	25	24 (96%)
B	178	163 (92%)
C	39	31 (79%)
D-E-F	21	19 (90%)
Total	263	237 (90%)

There is a marked preponderance of class B cases. White[6] has pointed out that difficulties of a special kind may arise in these apparently benign cases, e.g., "The shorter the duration of diabetes, and the less its degree, the greater the need for insulin during pregnancy," and, "In pregnancy the short-term diabetic is more susceptible to ketoacidosis than is the growth-onset patient. The ketoacidosis of pregnancy is treacherous, characterized by relative hypoglycemia; the blood glucose may be less than 200 mg. per 100 ml." Our experience is in complete agreement with these observations.

Insulin: Ninety-eight per cent of the patients were insulin-dependent. Three patients had been treated with sulfonylureas by their family doctors, but insulin was substituted immediately on reference to our care. Since 1954, we have used the Lente trilogy almost exclusively. Control has been uniformly good even in patients with a high daily requirement. The value of modifying the basic "readymade" Lente preparation by the addition of Semilente (amorphous) or by Ultralente (crystalline) should be appreciated. In a number of patients the insulin was tailored to individual requirements by using Semilente and Ultralente in combination (table 2).

TABLE 2

Example of insulin requirements during pregnancy in a diabetic

Maturity (wks.)	Dose of insulin	Blood glucose values (mg./100 ml.) Fasting	11 a.m.	11 p.m.
31	116S + 72U	56	50	106
32	116S + 72U	165	73	170
33	108S + 56U	105	118	100
34	100S + 44U	47	117	105
35	92S + 24U	109	75	61
36	76S + 20U	133	166	160

S = Semilente, U = Ultralente.

In recent years we have used Semilente insulin twice daily in the routine management of all young diabetics and this trend is reflected in pregnant diabetics. Thus, in the years 1961-65, of seventy-nine patients needing more than 40 U. per day, twenty-four were on a twice daily injection schedule. We have correlated certain aspects of insulin dosage with fetal survival. Sixty-five patients (25 per cent) had at some stage during pregnancy, a daily requirement in excess of 100 U. (table 3). The fetal survival in this group was similar to that in the remainder of the series. In 159 cases it was possible to compare prepregnancy insulin require-

TABLE 3

Outcome in sixty-five patients (25 per cent of series) needing more than 100 U. of insulin daily

Daily dose (U.)	No. of cases	Live infants
100 - 119	25	22 (88%)
120 - 139	17	16 (94%)
140 - 159	11	10 (91%)
160 - 232	12	11 (92%)
	65	59 (91%)

Infant survival in *remainder* of series = 89%.

TABLE 4

Outcome related to degree of change in insulin requirement (159 cases)

Pregnancy dose expressed as a percentage increase on "nonpregnant" dose	Infants	Live
Less than 100% increase	57	46 (81%)
100 to 200 % increase	59	52 (88%)
More than 200% increase	43	38 (88%)

ment with the maximum requirement during pregnancy. These cases were divided into three groups, depending on degree of change in requirement, as shown in table 4. Fetal survival is not influenced by change in insulin requirement, nor by the need for a large daily dose. It is the quality of diabetic control which is important, and not the dose of insulin necessary to obtain it.

Primigravidae: Anderson[7] reported that diabetic primigravidae lose more babies than diabetic multigravidae. This observation was not confirmed by Gellis.[8] In the present series there were forty-eight primigravidae (18 per cent of viables). The outcome of their pregnancies was forty-one live infants; four stillbirths and three neonatal deaths. Thus, the perinatal loss was 14.6 per cent by contrast with a 9.3 per cent loss in the multigravidae of this series. Harley and Montgomery[9] recorded a similar difference. The difficulty of inducing premature labor in primigravidae is well recognized, perhaps too much so. Induction was successful in twenty-one of twenty-nine attempts in this series (table 5). A more positive approach to induction in primigravidae would save many women from the primrose path of repeated sections.

TABLE 5

Method of delivery in primigravidae (48-3) (excluding three patients in whom spontaneous labor was awaited because of intrauterine death)

Spontaneous labor	11
Induction	21
Elective section	5
Nonelective section	8
Section rate for primigravidae	= 29%
Section rate for multigravidae	= 21%
Section rate for whole series	= 22%

Complications of pregnancy: It is generally accepted that complications of pregnancy are disproportionately common in diabetics, but the frequency varies considerably in published series. Thus, Kyle (Op. cit.) quotes eight published series with the incidence of hydramnios varying from 3 to 31 per cent, while in ten series published since 1953, the incidence of pre-eclamptic toxemia varied from 8 to 48 per cent. The main reason for these variations is different standards of definition. In addition, series differ considerably in the type (diabetic and social) of patient included; much will also depend on the proportion of booked cases in any given series. Hydramnios (a clinical diagnosis made by an experienced obstetrician) occurred in forty cases (15 per cent). Pre-eclamptic toxemia (defined as the occurrence of a blood pressure level of 140-90 on at least two occasions in association with either edema or albuminuria) occurred in thirty-nine cases (15 per cent). In ten cases hydramnios and pre-eclamptic toxemia were combined. The influence of these complications on fetal survival is shown in table 6.

TABLE 6

Outcome related to complications

Complication	No.	Live	Stillborn	Neonatal death	Per cent loss
Hydramnios	(30)	21	3	6	30
PET	(29)	26	1	2	10
Hyd. + PET	(10)	8	1	1	20
	69 (26%)	55	5	9	20

Loss for 192 uncomplicated cases was nine (5%)
Hydramnios in forty patients = (15%)
PET in thirty-nine patients = (15%)
Of perinatal losses with hydramnios, three had congenital defects.

It is significant that in 192 uncomplicated cases the fetal loss was 5 per cent, while in sixty-nine complicated cases the loss was 20 per cent. It is also of interest that of the fourteen infants lost in complicated pregnancies, nine died neonatally. Two had congenital defects incompatible with life (both mothers had hydramnios). The remaining seven died of respiratory-distress syndrome (six had hyaline membrane disease; one had atelectasis). It is tempting to speculate whether greater forbearance with regard to the timing of delivery in these patients would have given better results. However, failure to deliver infants quickly from an abnormal milieu might only transfer the death to the stillbirth column.

TABLE 7

Diabetic complications

Diabetic ketosis (12)	Hypoglycemic coma (21)
6 abortions + misc.	2 abortions
3 stillborn	1 stillborn at 36 wks. coma at 12 wks.
1 neonatal death	18 live (86%)
2 live (17%)	

Complications of diabetes: A policy of tight control of the diabetic state leads to a high incidence of hypoglycemic coma, and this complication was seen twenty-one times (table 7). This complication can cause considerable inconvenience to a patient living in a remote rural area, and we have found it useful to instruct husbands in the use of Dextrostix and in the administration of glucagon. Apart from its nuisance value, hypoglycemia (recognized and treated) is relatively innocuous by comparison with the deadly danger of ketosis to mother and fetus.

Severe ketosis occurred in twelve cases—all unbooked. In all but two cases the fetus died. Three of these women were gravely ill, and in one, a bilateral amputation at midfoot was a sequel to prolonged hypotension. In each of these three cases the patient's diabetes had not been recognized until they were referred to us in an unconscious state. All had been receiving antenatal care outside the hospital service.

It is vital for obstetricians to realize that pregnancy may uncover latent diabetes, and that glycosuria in pregnancy while usually benign, must not be presumed so.

Delivery: It is now our practice to deliver uncomplicated cases at thirty-eight-weeks maturity. However, each case must be assessed on its merits as timing of delivery is a matter of nice judgment based on experience. Table 8 details the relationship between fetal survival and maturity at delivery. In making the analysis, six perinatal deaths were excluded as they were unrelated to the timing of delivery. The low perinatal loss in ninety-one infants delivered at thirty-eight weeks or later is noteworthy, but the occurrence of three stillbirths in this group reminds us that there is the occasional price to be paid for maturity. These three stillbirths (table 12A) might have been avoided by earlier delivery—reinforcing the argument that, although general principles about the timing of delivery may be laid down, an individual decision has to be taken in every case.

TABLE 8

Outcome related to maturity at delivery

Maturity (wks.)	No.	Live	Still-born	Neo-natal deaths	Per cent loss
Before 36	(23)	19	2	2	17
36	(68)	64	0	4	6
37	(75)	66	2	7	12
38	(91)	88	3	0	3

Excluding 6 perinatal deaths: 4 Congenital defects; 1 Cytomegalic inclusion disease; 1 Maternal Lues Major + Bilat. active TB

Our belief that vaginal delivery is best for mother and child is evidenced by a section rate of 22 per cent for the whole series, and of 29 per cent for primigravidae. Table 9 relates fetal survival to method of delivery. To eliminate the factor of undue prematurity, four losses in patients delivered before thirty-six weeks were excluded; four losses due to congenital defects, and four intrauterine deaths were also excluded from this analysis. Of 182 infants delivered vaginally, twelve were lost (6.6 per cent), while of forty-nine delivered by cesarean section, two were lost (4.1 per cent).

TABLE 9

Outcome related to method of delivery in cases delivered at thirty-six weeks or later

Method	No.	Live	Still-born	Neo-natal deaths	Per cent loss
Spont. labor	(19)	18	1	0	6.6
Induction	(163)	152	2	9	
Elective C.S.	(23)	22	0	1	4.1
Nonelective C.S.	(26)	25	0	1	

Excluding 12 perinatal deaths: 4 Congenital defects; 4 Delivered before 36 wks. (30:33:35½:35½); 4 Intrauterine deaths

Kyle (Op. cit.) remarks that if too many babies are lost during vaginal delivery, the indications for cesarean section were not sufficiently broad. Analysis of the stillbirths in this series suggests that two might have survived if delivered by cesarean section (table 12B). Nevertheless, we are satisfied that a high section rate is by no means necessary in diabetics. Although many centers now "recognize" that vaginal delivery should be attempted more frequently, there is a tendency to be a little fainthearted in the attempt, and some recommend that cesarean section be performed if labor has not begun within six hours.

In this series the method of induction was by rupture of membranes followed twenty-four hours later by an oxytocin drip. If labor had not begun within forty-eight hours, cesarean section was performed. During this waiting period, the usual diet and insulin were continued. No difficulties arose from this policy of patient expectation.

The fact that infants of diabetics are often large is now well-known. In this series, sixteen infants weighed

TABLE 10

Weight in grams of 263 infants compared with mean weight of normal infants, after Streeter

Maturity (wks.)	Number of infants	Extremes of infant wgts. (gm.)	Mean wgt. (gm.)	Mean wgt. of normal infants (Streeter)
33	6	2,880 - 3,360	3,000	1,876
34	8	2,014 - 3,232	2,608	2,160
35	9	2,640 - 3,360	2,835	2,274
36	68	2,641 - 4,622	3,118	2,640
37	75	2,409 - 5,103	3,606	2,880
38	72	2,155 - 5,897	3,742	3,120
39	10	2,358 - 5,017	3,538	3,150
40	15	2,295 - 4,536	3,856	3,405

4,536 gm. or more. This is an incidence of 6.1 per cent by comparison with 1.3 per cent in the population as a whole. Table 10 compares the weights of infants in this series at various stages of gestation, with the average weights of infants born to normal mothers (Streeter[10]). The fact that the differences are greater in the earlier weeks may be accounted for by the fact that the presence of a big baby may be regarded as an indication for earlier delivery. Many of the infants were normal or undersized.

Congenital defects: It is widely recognized that congenital defects are common in infants of diabetic mothers. The frequency with which they have been reported varies from 2 to 5 per cent by comparison with an incidence of 0.74 to 1.7 per cent in a general population. In the present series, there were fourteen cases (5.3 per cent), table 11. Such cases make a contribution to the perinatal loss which will be difficult to eliminate.

TABLE 11

Fourteen cases with congenital defects in 263 viable infants (5.3 per cent)

3	Multiple defects (all died)
3	Congenital heart disease (1 died)
2	Talipes
1	Cyclops (died)
1	Mongol
1	Harelip + cleft palate
1	Spina bifida
1	Laryngomalacia
1	Hypospadias

Perinatal loss: An analysis of perinatal deaths is always chastening because the clarity of hindsight illuminates flaws in judgment and reasoning. Six of the ten stillbirths might have been avoided by alternative management, table 12B. Cases 5 and 10 should have been delivered by cesarean section. In Case 9, the size of the infant was not appreciated due to the fact that the mother weighed 200 pounds and was a grand multipara. Earlier delivery might have saved Cases 6, 7 and 8.

TABLE 12A

Four stillbirths — ? Unavoidable

(1) Mother had secondary Lues Major + bilateral acute exudative TB (IUD at 36 wks.)
(2) Infant showed evidence of cytomegalic inclusion disease (IUD at 38 wks.)
(3) Congenital defects incompatible with life (IUD at 36 wks.)
(4) Spontaneous labor at 33 wks.—Intraventricular hemorrhage

TABLE 12B

Six stillbirths—possibly avoidable by earlier delivery

(5) Induction delayed until 39 wks. because infant was small (2,353 gm.)—subdural hemorrhage during labor
(6) IUD at 35-5/7 wks. PET. Macerated (2,041 gm.)
(7) IUD at 37 wks. Macerated (2,325 gm.)
(8) IUD at 38 wks. Macerated (3,997 gm.)
(9) IUD at 37 wks.—infant size not appreciated (5,103 gm.)
(10) IUD at 38-3/7 wks. during spontaneous labor—transverse lie delayed induction—external cephalic version: marked shoulder dystocia. Macerated (4,649 gm.)

Three of the sixteen neonatal deaths were due to congenital defects. Three were due to intraventricular hemorrhage in small babies. Of these, one weighed only 964 gm.; one was a second twin weighing 2,070 gm. (induction at thirty-seven weeks) and the third weighed 1,503 gm. (induction at thirty-seven weeks), the estimate of fetal weight being greatly in error. Ten babies died with respiratory distress syndrome (RDS) (table 13). The role of prematurity and of delivery by cesarean section in the production of RDS has always excited controversy. In this series of fifty-six living

TABLE 13

Respiratory-distress syndrome (10)

Maturity (wks.)	Weight (gm.)		
35½		2,880*	
36	3,689		2,880
36-37	3,085		2,949
37-38	2,785		3,448
	3,721*		2,323
		3,629*	

*Cesarean section

54 living infants were delivered by C.S.—3 RDS (5.6 per cent).

196 living infants were delivered vaginally—7 RDS (3.6 per cent).

infants delivered by cesarean section, three developed RDS (5.3 per cent), while of 197 living infants delivered vaginally, seven developed RDS (3.5 per cent). This difference is not statistically significant.

RDS represents the "sound barrier" in the care of the pregnant diabetic, and presently makes the greatest contribution to perinatal loss. The fact that seven of the ten cases of RDS occurred in complicated pregnancies has already been noted. These infants were reasonably mature by weight and dates and yet succumbed. Does this support the view that RDS is begotten in utero? If so, then it would appear that the greatest single contribution to be made to the reduction of perinatal loss lies in the prevention of toxemia and hydramnios.

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BRIEF NOTES AND COMMENTS

Effect of Antagonistic Albumin on Insulin-stimulated Intracellular Metabolic Pathways

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SUMMARY

Previous data on incorporation of glucose C-14 into glycogen by the rat diaphragm had suggested that this synthetic pathway was unaffected by the albumin-associated insulin antagonist. To test the hypothesis that only the transport functions of insulin were blocked by this antagonist, studies on two insulin-stimulated intracellular pathways independent of transport were carried out. The increase in tissue levels of the I form of glycogen synthetase seen with insulin was not affected by antagonistic albumin (human fraction V). The D form of glycogen synthetase was also unaffected. However, insulin-stimulated adenine-8-C-14 incorporation into RNA was completely abolished by this albumin. A nonantagonistic albumin (bovine fraction V) by itself increased RNA synthesis indicating that the inhibition of insulin-stimulated RNA synthesis was not a general property of the albumin molecule. The physical-chemical and metabolic characteristics of the albumin-associated antagonist are summarized and are considered to be incompatible with the postulated physiological role for this insulin antagonist. DIABETES 15:835-38, November, 1966.

We recently published a paper[1] in this journal on the mechanism of insulin antagonism by albumin on rat diaphragm. These studies indicated that antagonistic albumin was bound to the diaphragm and blocked insulin-stimulated transport of glucose and AIB in a noncompetitive manner. Data on glycogen synthesis suggested that this pathway was relatively unaffected by the albumin antagonist. Thus: (1) Although human fraction V by itself depressed basal glucose uptake slightly, it increased glucose-C-14 incorporation into glycogen by 118 per cent; (2) in spite of a marked reduction of insulin-stimulated glucose uptake by albumin, 92 per cent of this decreased uptake was channelled into glycogen synthesis; and (3) although glycogen synthesis was stimulated

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