Pregnancy in insulin-dependent diabetics

A 5 1/2-year study at Groote Schuur Hospital

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Summary

During a 5 1/2-year period we have seen only 39 pregnant women with insulin-dependent diabetes, as opposed to 171 with established insulin-independent diabetes. Tight control with two injections of mixed insulins per day was attempted, but satisfactory blood glucose values were obtained in only 16 cases. Nevertheless the overall perinatal mortality rate was 77/1000; of the 3 infants which died 2 had lethal congenital abnormalities and 1 was born to a mother whom we had been seeing for only 4 weeks.

Perinatal morbidity was similar to that in other series, except that few of our infants were oversized, hyaline membrane disease was uncommon, and only 2 had a low Apgar score. Fourteen infants weighed less than 2500 g. Hypoglycaemia in the newborn appears to be much reduced by the use of continuous low-dose intravenous insulin infusion during labour or caesarean section.

To reduce perinatal mortality further, we conclude that exact blood glucose control should be attained before conception.


TABLE I. COMPARISON BETWEEN INSULIN-DEPENDENT AND INSULIN-INDEPENDENT DIABETICS SEEN OVER A 5 1/2-YEAR PERIOD

<table>
<thead>
<tr>
<th></th>
<th>Insulin-dependent</th>
<th>Insulin-independent*</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>39</td>
<td>171</td>
</tr>
<tr>
<td>Whites (%)</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Obese (%)</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>25.7</td>
<td>32.5</td>
</tr>
<tr>
<td>Mean infant birth weight (g)</td>
<td>2700</td>
<td>3250</td>
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* Excluding women with gestational diabetes.
Insulin-dependent (juvenile-onset or type I) diabetes was considered to be present in patients who had a history of ketoadisosis, who had received insulin since childhood, or whose diabetic symptoms had not been controlled by proper dieting and hypoglycaemic agents before pregnancy.

Since we believe weight control to be important during pregnancy, as discussed elsewhere, patients who were more than 20% overweight generally received a 5000 kJ (1200 kcal) diet, while subjects of 'normal' weight (i.e. less than 10% overweight) were allowed 6700-7600 kJ (1600-1800 kcal). Patients whose pregnancies continued to term were managed by us for periods varying between 4 and 28 weeks before delivery.

### Diabetes control

Capillary blood samples were taken at least 5 times daily, at 06h00, 11h00, 14h00, 18h00 and 20h00. Blood was collected into microtubes containing fluoride and heparin and centrifuged, and the plasma glucose level was estimated with a Beckmann glucose analyser.

If the patient's diabetes was clearly out of control, soluble insulin (more recently Actrapid insulin) was given before each of the three main meals, the dose depending on a Dextrostix estimation of the blood glucose level (e.g. 10 U for 90-130 mg/dl; 20 U for 130-175 mg/dl; 30 U for 175-250 mg/dl and 40 U for > 250 mg/dl).

The range of insulin dosage was increased if required and a fourth dose given before the evening snack. As soon as some measure of control was achieved the insulin was changed to a fixed dose, given twice daily (before breakfast and before supper) in a ratio of approximately 3:2. Intermediate-acting insulin (initially isophane or neutral protein Hagedorn (NPH); more recently Monotard) was then added to the soluble insulin, to the morning dose if the blood glucose level was high in the afternoon, or to the evening dose if the blood glucose level was high during the night and early morning. The dose of soluble insulin was also adjusted according to the blood glucose readings within the first 6 hours or so after the injection. Occasionally a third injection of soluble insulin was given before lunch.

The control achieved after the initial balancing period was classified as follows: excellent — virtually all blood glucose readings < 6.7 mmol/l (120 mg/dl); good — virtually all blood glucose readings < 7.8 mmol/l (140 mg/dl); moderate — virtually all blood glucose readings < 8.9 mmol/l (160 mg/dl); poor — readings frequently > 8.9 mmol/l (160 mg/dl).

The urine was regularly tested with Ketostix, and blood ketone concentrations were determined when the Ketostix reading was repeatedly 2+. Dietary adjustments were made according to the results.

When the patient's plasma glucose profile was satisfactory she was discharged and followed up at the diabetes antenatal clinic, where frequent random determinations of the blood glucose level were made to detect any worsening in the control. If this occurred the patient was readmitted. In some instances patients estimated their own blood glucose values using Dextrostix, alone or with an Eyetone reflectance meter.

From 32 weeks' gestation all patients were readmitted for strict control of the plasma glucose level, tests for fetal well-being (human placental lactogen and serial ultrasound diameter estimation, charting of fetal movement, and non-stressed cardiotocography) where indicated, and bed rest.

### Results

During the period June 1974 - February 1980, 39 pregnant insulin-dependent women were seen and managed by us. The mean age was 25.7 years, 28 were of 'normal' weight (Table I), and 19 were primigravidas. Sixteen patients fell into the Priscilla White group B, 19 into group C, 3 into group D and 1 into group F. Estimated control of the diabetes was excellent in 9 and poor in 12 (Table II). The insulin dose at term was generally greater than that when the patient was first seen by us (mean values 72.6 U/d and 97.2 U/d), but in 2 subjects the dose was substantially reduced (see 'Special cases' below).

Two spontaneous abortions occurred, 1 pregnancy was terminated, and there were 2 pairs of twins. Of the 38 remaining viable infants none was stillborn, but 3 died in the neonatal period, 2 because of severe congenital anomalies (1 holoprosencephaly and 1 congenital heart defect). The other neonatal deaths occurred in a premature infant of 32 weeks' gestational age whose mother had been with us for only 4 weeks. Her insulin dose had been increased from 50 to 145 U/d but her diabetes remained poorly controlled. An elective caesarean
section was performed when meconium was found in the amniotic fluid. The overall perinatal mortality rate was therefore 77/1 000; 0/1 000 if we consider only infants born to mothers seen for more than 4 weeks and exclude those with congenital abnormalities.

The mean birth weight was 2 800 g (excluding twins) (Table III). Three infants (8%) had major congenital abnormalities; 2 (5%) had lethal anomalies, as mentioned above, and 1 hypoplasias and talipes equinovarus.

<table>
<thead>
<tr>
<th>TABLE III. DATA ON 38 VIABLE INFANTS</th>
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<tr>
<td>Stillbirths</td>
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<td>Neonatal deaths</td>
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<td>Mean birth weight</td>
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<tr>
<td>Congenital abnormalities</td>
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<td>Hypoglycaemia</td>
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Perinatal morbidity

Hypoglycaemia. Five neonates (13%) in this study developed hypoglycaemia, defined as a blood glucose level below 25 mg/dl (1.4 mmol/l) (Dextrostix) measured any time during the first 48 hours.

Hyaline membrane disease (HMD). A diagnosis of HMD was made according to the following criteria; respiratory rate > 60/min; expiratory grunting; subcostal, sternal and intercostal recession; cyanosis in room air; reduced air entry; a chest radiograph showing an air bronchogram and a reticulogranular pattern at 6 hours of age. Two infants developed HMD. Both had a 2+ foam score, but in 1 there was meconium in the liquor amnii. This infant was one of the neonates which died.

Hyperbilirubinaemia. Neonates were considered to have significant hyperbilirubinaemia if the serum bilirubin level was above 10 mg/dl (170 mmol/l). Eighteen percent (7 of the 38) had hyperbilirubinaemia by these criteria.

Polycythaemia. Two neonates had haematocrit values above 70%.

Macrocosmia. Five neonates (14%) weighed above the 90th percentile for their gestational age and were considered macroscopic or large for gestational age (LGA). Only 1 weighed more than 4 000 g. The birth weight chart used is based on the local population.

Low birth weight. Fourteen (37%) neonates, including 1 pair of twins, weighed less than 2 500 g (low birth weight). Three (8%) weighed below the 10th percentile for their gestational age and were considered small for gestational age (SGA), and the rest had weights which were considered appropriate for gestational age (AGA). The gestational age of 2 of these infants was over 35 weeks, the other 9 being preterm. Spontaneous rupture of the membranes made delivery of 2 of the preterm infants mandatory, and in 1 case the fetus was thought to be SGA; on delivery it was found to have holoprosencephaly, and it died soon after birth. In 1 case meconium in the liquor amnii was the reason for early delivery. In the remaining 5 cases (1 pair of twins) the gestational age was thought to be at least 36 weeks and the foam score confirmed pulmonary maturity. HMD did not develop in any of the infants in this last group, but 1 died because of a congenital heart defect. The infant which was delivered because of meconium in the liquor amnii died of HMD.

Low Apgar score. Only 2 neonates had 5-minute Apgar scores of 6 or below.

Special cases

In 2 cases there was a fall in insulin requirements during pregnancy.

1. A 20-year-old Black diabetic woman of normal weight, who had been on insulin for 6 years, was seen at 28 weeks' gestation. Her diabetes was poorly controlled on 105 U insulin per day. She was moderately controlled at term on 50 U/d. The baby, delivered by caesarean section and weighing 3 280 g, did well; the patient had had one previous baby, which died in the neonatal period.

2. A 23-year-old Coloured diabetic woman of normal weight, who had been on insulin for 8 years, had had 3 previous spontaneous abortions. Control of her diabetes was moderate on 70 U insulin per day at 9 weeks' gestation; at term control was good on 40 U. The baby, born by caesarean section and weighing 2 880 g, did well.

Discussion

Control of diabetes

We work on the generally accepted principle that control of the blood glucose level during pregnancy should be extremely strict, even at the risk of occasional hypoglycaemic reactions. The latter should not, of course, be severe enough seriously to inconvenience the mother or to produce unconsciousness. We find, as have others, that the twice-daily combination of a rapid-acting and an intermediate-acting insulin generally produces reasonable control, although a third injection of rapid-acting insulin before lunch may occasionally be needed. The highly purified monocomponent insulins are preferred, although they are certainly not essential, for two reasons: (i) the lack or near-lack of antibody stimulation (whether this really matters, however, is not clear); and (ii) the lack or near-lack of cutaneous reactions to insulin.

Home monitoring of blood glucose levels can be very useful in improving control and reducing the need for admission to hospital, although obviously some skill and understanding on the part of the patient are required. Small 'pocket' glucose estimators are now available in this country.

Insulin requirement usually, but not always, increases during the second half of pregnancy; occasionally it may be reduced, as in the 2 cases mentioned above, and rarely a true remission occurs. Some reduction in insulin requirement may be explained by better adherence to the recommended diet.

Correct eating patterns are equaly important. We believe that weight control is as advisable in insulin-dependent as in insulin-independent diabetics, and we use diets ranging from 5 000 to 8 400 kJ per day, divided into 3 main meals and 3 intermediate snacks. We tend to increase the carbohydrate content of the late-night snack if strongly positive ketonuria persists in the early morning. Nevertheless we have never found Ketostix tests to be positive in the plasma or dangerous levels of ketone bodies in the blood on laboratory estimation.

It is clear that the diabetes control we achieved was not as good as we would have liked (Table I). The reasons for this are: (i) patient presentation too late in pregnancy for the best control to be attained; (ii) unsatisfactory patient compliance; (iii) the inherent impossibility of obtaining excellent control in all patients by routine methods because of variable absorption of insulin, variable absorption of food from the gut, variable availability of circulating insulin, and other factors; and (iv) imperfect prescription of insulin or of food or imperfect carrying out of these orders.

It is possible that continuous subcutaneous delivery of low-dose insulin may produce better control in some patients, but it may be asked whether this is necessary. It would seem doubtful whether, except with regard to congenital abnormalities, it is possible further to reduce perinatal mortality or even perinatal morbidity in infants born to mothers who present reasonably early in pregnancy and who are reasonably compliant.
Perinatal morbidity

The numbers in this series are small, but the paucity of insulin-dependent compared with non-insulin-dependent patients dramatically illustrates the different composition of diabetics in the Cape Town population compared with the Western world.\textsuperscript{14,15} However, the pattern of perinatal morbidity is almost identical to that in infants born to non-insulin-dependent diabetics in our series\textsuperscript{2,16} and those of others,\textsuperscript{13,15} hypoglycaemia, hyperbilirubinaemia and congenital abnormalities being major problems. Of special note is the higher prevalence of congenital abnormalities reported in this series compared with our non-insulin-dependent groups,\textsuperscript{14,15} in which many mothers had received oral hypoglycaemic drugs in the first trimester of pregnancy.

It is thought at present that congenital abnormalities are frequent in infants of diabetic mothers because of poor control of the blood glucose level during the first 14 weeks of pregnancy. There is some indirect evidence for this. Dr Kitzmiller of the Joslin Clinic, Boston, USA (personal communication) found an increased incidence of congenital abnormalities in infants born to patients who had an elevated haemoglobin A\textsubscript{1c} in the first trimester, reflecting poor control of blood glucose levels. If this is true, tight control of the diabetes should be required before the patient becomes pregnant. In other words, pregnancy in diabetics should be planned and the best possible control achieved before conception, with admission to hospital if necessary.

The incidence of hypoglycaemia could be reduced by the use of continuous low-dose intravenous insulin plus glucose infusion during labour or caesarean section.\textsuperscript{7,16} This regimen maintains the mother's blood glucose level within the physiological range and prevents overstimulation of the infant's pancreas. Labour can be allowed to proceed for longer than in the past, and the incidence of fetal distress may be reduced.\textsuperscript{12}

One difference between this series and our own and other previously published series is the normal distribution of LGA infants to patients who had an elevated haemoglobin A\textsubscript{1c} in the first trimester of pregnancy. It is thought at present that congenital abnormalities are partly be due to overenthusiastic induction of labour, but most of these infants had mature lungs and did not behave like infants of diabetic mothers. Birth weights are lower in infants born to young Coloured mothers.\textsuperscript{14} This may be a socio-economic factor, but in our older obese, insulin-independent diabetic mothers larger babies are the rule even when the mother is strictly dieted.\textsuperscript{14} Fetal maturity in general, and pulmonary maturity in particular, are accelerated in the Coloured population.\textsuperscript{19} This observation is supported by our own data; only 2 of the low-birth-weight infants were White, and both were SGA. Of the 10 AGA low-birth-weight infants 9 had mature lungs at birth. Of the 2 infants which developed HMD, 1 was White, weighed 2550 g, and had a gestational age of 36 weeks. The only coloured neonate to develop HMD weighed 1460 g, had a gestational age of 32 weeks, and was delivered because meconium was found in the amniotic fluid. The amniocentesis was done because this pregnancy was 37 weeks by dates. Although a foam score of 2+- was obtained, we now realize that meconium and blood may invalidate this test.\textsuperscript{20}

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REFERENCES