with acute myeloid leukaemia is of great clinical importance. Water intoxication may produce confusion (Kaye, 1966) and disorientation (Weissman *et al.*, 1971)—symptoms which can readily be confused with the terminal state of acute leukaemia. Intravenous infusion can be hazardous in these patients. Attention to the underlying electrolyte imbalance will lead to the correct diagnosis, which is reversible by water restriction.

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Remission of Diabetes Mellitus during Pregnancy

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Summary

Two cases are reported in which a remission of diabetes was sustained throughout pregnancy. This seemed to be due in part to improved β -cell function consequent on restoration of normoglycaemia before pregnancy, and in part to an increase in insulin sensitivity during pregnancy, which in the first case disappeared very rapidly after delivery.

Introduction

Though partial remission of diabetes is not uncommon in young diabetics soon after control has been established the return to normal glucose tolerance is rare (Harwood, 1957; Peck *et al.*, 1958; Stutman and Hayes, 1959; Hines and Kessler, 1961; Field *et al.*, 1961; Brereton, 1968). For glucose tolerance to remain normal throughout pregnancy in a diabetic is even more remarkable. It seemed of interest, therefore, to report two cases in which remission of diabetes persisted during pregnancy, the response to 50-g oral glucose tolerance tests remaining normal throughout in one and nearly normal in the other.

Case 1

This patient was found to be a diabetic at the age of 29 when she presented with a three-month history of recurrent boils. There were no other symptoms and she was of normal weight. The blood glucose in the mid-morning at her first clinic visit was 302 mg/100 ml (G.O.D. period method, Boehringer). After one month on a 150-g carbohydrate diet her mid-morning blood glucose was 334 mg/100 ml. She was therefore given chlorpropamide 250 mg daily (fig. 1). After starting chlorpropamide, and until after delivery, all mid-morning blood glucose values were below 120 mg/100 ml (mean

FIG. 1—Case 1. Mid-morning blood glucose values over two-year period. Readings taken two to three hours after a meal.

83 mg/100 ml). All urine tests done twice daily throughout pregnancy were negative for sugar. Chlorpropamide was discontinued at 32 weeks of pregnancy. Between the 33rd and 37th weeks four 50-g oral glucose tolerance tests were done (table I). The highest one-hour value was 173 mg/100 ml and the highest two-hour value 123 mg/100 ml. (A 100-g oral glucose tolerance test at 35 weeks, however, produced a two-hour blood glucose of 175 mg/100 ml, and response to a cortisone glucose tolerance test (Fajans and Conn, 1961) was grossly abnormal at 38 weeks). Serum insulin (Hales and Randle, 1963) was low throughout all these tests for this stage of pregnancy. Plasma placental lactogen (Letchworth *et al.*, 1971) estimated during each test was within the normal range (table I). Twenty-four-hour urinary oestriol (Brombacher *et al.*, 1968) measured on 11 occasions from the 32nd week was also normal, ranging from 10.5 to 44.3 mg/24 hours.

Glycosuria reappeared four days after delivery and glucose tolerance deteriorated rapidly thereafter (fig. 2).

The baby, delivered at 38 weeks, was a typical infant of a diabetic mother, weighing 4,360 g at birth. The placenta was also a little heavy (51 g). The baby rapidly became hypoglycaemic, cord blood glucose dropping from 88 mg/100 ml at birth to less than 10 mg/100 ml one hour later, when an intravenous glucose infusion was started. In spite of a continuous glucose infusion and glucagon

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TABLE I—Case 1. 50-g Oral Glucose Tolerance Tests at 33-37 Weeks

Time (hr):	Blood Glucose (mg/100 ml)				Serum Insulin (pU/ml)				Placental Lactogen (pg/ml)			
	0	$\frac{1}{2}$	1	2	0	$\frac{1}{2}$	1	2	0	$\frac{1}{2}$	1	2
33 Weeks	56	104	124	103	—	—	—	—	—	—	—	—
34 "	50	—	173	115	7	19	15	17	5.4	5.7	5.5	6.2
36 "	61	100	153	123	4	13	15	14	3.5	4.5	5.4	5.5
37 "	39	101	123	85	4	16	12	9	8.4	7.0	7.8	8.8

FIG. 2—Case 1. Response to 50 g oral glucose tolerance tests 8 days (I), 9 days (II), and 21 days (III) after delivery. Dotted line indicates mean of four tests at 33-37 weeks of pregnancy. F... Fasting.

the baby remained hypoglycaemic for four days. Serum insulin, measured on two occasions during this hypoglycaemic phase, was only 10 and 7 μ U/ml.

Case 2

This patient was found to be diabetic at the age of 33, again presenting with recurrent boils. She was obese, weighing 113 kg. The blood glucose was 271 mg/100 ml in the mid-morning at her first clinic visit, and she was put on a 1,000-calorie diet and slow-acting phenformin 50 mg/day (fig. 3). All urine tests done twice daily throughout pregnancy were negative for sugar. Phenformin was stopped at eight weeks of pregnancy by which time she had lost 14 kg. Tolerance tests with 50 g oral glucose were performed at 25, 30, and 37 weeks (table II). The highest two-hour blood glucose value was 125 mg/100 ml at 37 weeks, though a 100-g oral glucose tolerance test at this time gave a two-hour value of 175 mg/100 ml. Her serum insulin was low during these tests for this stage of pregnancy. Twenty-four-hour urinary oestriol at the 33rd and 38th weeks was normal at 25 and 48 mg/24 hours, as was urinary free cortisol (Mattingly, 1962) at 37 weeks. Placental lactogen was nor-

FIG. 3—Case 2. Mid-morning blood glucose values over 19 months from time of first clinic visit. Readings taken two to three hours after a meal.

TABLE II—Case 2. Results of 50-g Oral Glucose Tolerance Tests at 25, 30, and 37 Weeks

Time (hr):	Blood Glucose (mg/100 ml)				Serum Insulin (pU/ml)			
	0	$\frac{1}{2}$	1	2	0	$\frac{1}{2}$	1	2
25 Weeks	94	162	151	107	36	47	53	34
30 "	77	131	178	104	20	36	28	24
37 "	87	144	188	125	16	20	34	25

mal at 5.7 μ g/ml at 37 weeks. Fasting plasma glucagon (Bloom, 1972) was 140 pg/ml at 37 weeks, which is in the normal non-pregnant range. Plasma chorionic gonadotrophin (Wylde *et al.*, 1967) was 10.8 IU/ml at 37 weeks.

The infant was overweight at 4,470 g and rapidly became hypoglycaemic, the cord blood glucose falling from 111 mg/100 ml at birth to 18 mg/100 at one hour. Blood glucose values became normal by the third day. An intravenous glucose tolerance test, using 0.5 g glucose/kg starting one hour after birth, gave serum insulin values of 18, 100, 68, and 19 μ U/ml before and at 2, 5, and 30 minutes after the glucose load. These insulin values were low by comparison with figures obtained from infants of diabetic mothers not treated with insulin (Isles *et al.*, 1968).

Discussion

Blood glucose and insulin values in the 50-g oral glucose tolerance tests in these two patients during pregnancy were compared with the mean values obtained in 15 non-diabetic pregnancies at 32 weeks by Campbell *et al.* (1971). Blood glucose rose a little higher in both our patients than in these non-diabetics but was nevertheless within the generally accepted normal range in case 1 and almost within it in case 2. Both patients, however, had insulin values much lower than the mean values obtained by Campbell *et al.*, indicating insulin deficiency.

The association of such low serum insulin values with virtually normal glucose tolerance indicates a degree of insulin sensitivity remarkable in the pregnant diabetic, in whom insulin antagonism usually develops (Kalkhoff *et al.*, 1964).

It seems likely that in these two patients β -cell function improved before they became pregnant as a result of the maintenance of normoglycaemia consequent on diet and chlorpropamide in the first case, and diet—with appreciable weight loss—and phenformin in the second. An increased insulin response to glucose is known to occur in mild diabetics as blood glucose levels are reduced by carbohydrate restriction (Rudnick and Taylor, 1965) or sulphonylurea treatment (Sheldon *et al.*, 1966). Towards the end of pregnancy, however, both patients showed evidence of increased insulin sensitivity, which was particularly evident in case 1. This seemed likely to be due to some factor specifically associated with pregnancy, as glucose tolerance in this case deteriorated so rapidly after delivery. For this reason it seemed unlikely to be related to the previous chlorpropamide treatment. There was, however, no evidence that this increased sensitivity to insulin was due to deficiency of placental lactogen or cortisol. In case 2 plasma glucagon at term was normal by non-pregnant standards, and oestriol excretion was within the normal range in both patients. The nature of their increased insulin sensitivity remains obscure.

Both infants were overweight and both developed neonatal hypoglycaemia, which was particularly severe and prolonged in case 1 in spite of maternal blood glucose levels having remained normal or near normal throughout pregnancy. Insulin values in these babies were low, suggesting that they too may have been unusually sensitive to insulin rather than that their hypoglycaemia was due to fetal hyperinsulinism, which is the usual explanation for hypoglycaemia in infants of diabetic mothers, being a consequence of maternal hyperglycaemia.

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ADDENDUM.—Since submitting this paper for publication one of these patients (case 1) again became pregnant. Her diabetes improved progressively during pregnancy and at 37 weeks a 50-g oral glucose tolerance test gave blood sugars when fasting and half an hour, one hour and two hours after glucose of 53, 98, 102, and 138 mg/100 ml. The chlorpropamide was discontinued at 34 weeks. At 38 weeks she was delivered by caesarean section of an infant weighing 4,650 g which died at birth. There was gross hypertrophy and hyperplasia of the fetal islets, which presumably was not consequent on maternal hyperglycaemia but was possibly due to the chlorpropamide treatment. Once again her diabetes deteriorated rapidly immediately after delivery. The fasting blood sugar two days after delivery was 195 mg/100 ml.

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Vitamin A, Pregnancy, and Oral Contraceptives

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Summary

It has been shown that women receiving oral contraceptives have increased levels of serum vitamin A. High vitamin A levels may constitute a teratogenic hazard and it has been suggested that women who conceive soon after discontinuing oral contraceptive therapy may be especially at risk to this hazard.

We have confirmed a significant increase in vitamin A levels in women taking oral contraceptives. During early pregnancy there is no significant difference in vitamin A levels between women who have recently been taking oral contraceptives and those who have not. We have been unable to show that either taking oral contraceptives shortly before pregnancy or a high vitamin A level during the first trimester of pregnancy, comparable to that of a woman taking oral contraceptives, has any detrimental effect on the outcome of pregnancy. It seems unlikely that women who conceive soon after discontinuing oral contraception run any teratogenic risk from increased vitamin A levels.

Introduction

Since the introduction of synthetic steroids as a method of birth control there have been numerous reports of side effects and alterations in biochemical values among women taking these preparations. Gal *et al.* (1971) noted a significant increase in plasma vitamin A in women taking oral contraceptives. Briggs

et al. (1972) also showed that women taking oral contraceptives had a significantly higher plasma vitamin A level than untreated controls, whereas the vitamin A levels of women receiving a long-acting, parenterally-administered progestogen contraceptive were similar to control values.

The importance of this lies in the possible teratogenic effect of excess vitamin A. Several workers have shown that the administration of large doses of vitamin A to pregnant animals may be associated with an increased incidence of congenital malformations (Cohlan, 1954; Giroud, 1960). This effect is enhanced by cortisone (Woollam and Millen, 1960).

In the field of human teratology, Pilotti and Scorta (1965) described a case of hypervitaminosis A in an Italian woman. She ingested excessive amounts of vitamins A and D (40,000 and 600,000 IU respectively) daily for a month at the beginning of pregnancy and gave birth to a child who at necropsy showed malformations of the urogenital system.

Gal *et al.* (1972) found significantly higher postpartum serum vitamin A levels in mothers of children with defects of the central nervous system than in mothers of normal children. Their study was retrospective, however, and the authors themselves pointed out the need to determine whether the high serum vitamin A level is present in early pregnancy and could be a primary cause of malformations or whether it is a secondary response to the presence of a malformed fetus. If a high serum vitamin A level can be a primary cause of malformations, and if the vitamin A level remains high after stopping oral contraception, then those women who conceive immediately after stopping oral contraception may run an increased risk of bearing malformed children. We have had the opportunity to study the serum vitamin A levels of women in early pregnancy, to relate these to the administration of oral contraceptives immediately preceding conception, and to observe the outcome of the pregnancies.

Subjects and Methods

As part of a large-scale, prospective study of nutrition in early pregnancy blood samples were taken from several hundred mothers in the first 15 weeks of pregnancy for analysis of several

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