IMPORTANCE OF ABNORMAL GLUCOSE TOLERANCE (HYPOGLYCÆMIA AND HYPERGLYCÆMIA) IN THE ÆTIOLOGY OF PRE-ECLAMPSIA

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Summary In a series of 794 patients who had glucose tolerance tests done before the onset of pre-eclampsia, both hypoglycæmia (<5th percentile) and hyperglycæmia (≤95th percentile) had a significant association with early-onset severe pre-eclampsia ($P<0.05$). In the total series of 794 patients, hypoglycæmia had a significant association with low œstriol excretion ($P<0.01$), fetal growth retardation ($P<0.05$), low Apgar score ($P<0.05$), and perinatal mortality ($P<0.05$). These data indicate that, in patients with pre-eclampsia, hypoglycæmia is directly related to the cause of perinatal death.

Introduction

DIABETIC women in pregnancy often become pre-eclamptic. Because of this, pre-eclampsia has been regarded as an indication for testing glucose tolerance,[1] and it has been suggested that a number of perinatal deaths attributed to pre-eclampsia may have been due to unrecognised diabetes.[2] Despite this, it is not known whether hyperglycæmia is directly involved in the ætiology of pre-eclampsia. A significant association has been shown between maternal hypoglycæmia and fetal growth retardation.[3] Pre-eclampsia is associated with fetal growth retardation, especially when the disease is severe and accompanied by proteinuria. This suggests that there may be an association between pre-eclampsia and hypoglycæmia.

Singh[4] found that 15 patients with severe pre-eclampsia had significantly low fasting glucose levels, possibly caused by impaired hepatic gluconeogenesis. He concluded that the incidence of diabetes was higher in these patients, and suggested that carbohydrate metabolism in severe pre-eclampsia was altered by maternal β-cell hypoxia caused by vascular changes. Glucose tolerance tests were done after the patients had acquired the signs of pre-eclampsia.

We consider that maternal hyperglycæmia and hypoglycæmia are more likely to precede the onset of pre-eclampsia than to be a consequence of it. This paper reports the findings in 794 patients who had glucose tolerance tests done before they had signs of pre-eclampsia.

Materials and Methods

At the Mercy Maternity Hospital, Melbourne, many patients are screened with a glucose tolerance test between 32 and 34 weeks of gestation. During the period from March, 1971 until January, 1975 12 924 patients were delivered at this hospital and pre-eclampsia was diagnosed in 1316 (10·2%). Pre-eclampsia was diagnosed when at least two of the signs, hypertension 140/90 mm Hg or above, generalised œdema, and proteinuria not due to urinary infection or contamination, were present after the 20th week of gestation. The high incidence of pre-eclampsia in this series was due to inclusion of patients who acquired these signs during labour. The spectrum of severity of the disease was wide and patients were grouped according to whether the diagnosis was made before or after the beginning of the 37th week of gestation, and according to the presence or absence of proteinuria.

Glucose tolerance tests were done in 817 of the 1316 patients with pre-eclampsia (62·1%). The test was unavoidably omitted from unbooked patients who were admitted to hospital in labour or with severe disease requiring immediate delivery, and in booked patients who contracted severe pre-eclampsia before 32 weeks of gestation. The test was more often omitted in private patients because of administrative reasons. From the 817 patients 23 with multiple pregnancies were excluded to avoid confusion of results which might more correctly relate to the abnormal pregnancy rather than to abnormal carbohydrate metabolism. The results obtained in the remaining 794 patients were analysed. These patients all had a standard 50 g oral glucose tolerance test done between 32 and 34 weeks of gestation. Patients continued their normal diet but fasted from 10.00 P.M. on the night before the test, which commenced at 9.00 A.M. Capillary blood was obtained by finger prick and plasma-glucose was assayed by the glucose-oxidase method with a Beckman glucose analyser. Plasma-glucose was measured on a fasting specimen and 1, 2, and 3 hours after the ingestion of glucose. The fifth and ninety-fifth percentiles for plasma-glucose in the fasting 1, 2, and 3 hour specimens were derived from an analysis of the first 5000 glucose tolerance tests performed at the hospital.[3] These values are shown in table I. Hypoglycæmia was diagnosed when the plasma-glucose

TABLE I—DEFINITIONS OF HYPOGLYCAEMIA AND HYPERGLYCAEMIA

—	Plasma-glucose (mg/dl)			
	Fasting	1 h	2 h	3 h
Hypoglycæmia—5th percentile	65 (3·6)	90 (5·0)	70 (3·9)	55 (3·0)
Hyperglycæmia—95th percentile	95 (5·3)	170 (9·4)	130 (7·2)	105 (5·8)

Figures in parentheses denote mmol/l.

equalled or was less than the fifth percentile on any of the four plasma-glucose measurements. Hyperglycæmia was diagnosed when the plasma-glucose equalled or exceeded any of the four ninety-fifth percentiles. Normoglycæmia was defined as being present when all four glucose levels during the tolerance test fell within the fifth to ninety-fifth percentile ranges. Diabetes was diagnosed when the 2-hour plasma-glucose value was 140 mg/dl (7·8 mmol/l) or more and a value of 180 mg/dl (10 mmol/l) or more was recorded at any time during the test.

Urinary œstriol excretion was measured by the method of Brown et al.[5] and was regarded as low when one or more values were obtained below a line joining 8 mg/24 h (27·8 μmol/24 h) at 30 weeks and 12 mg/24 h (41·6 μmol/24 h) at 40 weeks of gestation.

Infants were diagnosed as small for dates (fetal growth retardation) when the birth-weight was below the tenth percentile and large for dates when this was above the ninetieth percentile according to gestational age for infants born in this community.[6]

Results

Pre-eclampsia and Hyperglycæmia

In this study 23·8% of patients (189 of 794) had early-onset pre-eclampsia; in this group the incidence of proteinuria was 59% whereas it was only 39% in the much larger (605 of 794) late-onset group (table II). As would be expected most of the patients who first had

the signs of pre-eclampsia in labour (260 of 271) were in the late-onset group.

The important finding was a statistically highly significant increase in the incidence of hyperglycæmia in patients with the most severe form of pre-eclampsia—i.e., those with early-onset disease associated with proteinuria. In this group the incidence was 21·4%, compared with 11·7% for the hospital population (table II) ($P<0.01$). Also the tendency towards hyperglycæmia within this group with early-onset severe pre-eclampsia was more marked in multiparæ (25·6%) than in primiparæ (19·2%). There was also a significant increase in the incidence of hyperglycæmia in multiparæ with late-onset mild pre-eclampsia (table II) ($P<0.05$).

6 patients had diabetes and 4 of the 6 were multiparæ. There was no difference in the incidence of diabetes in patients with pre-eclampsia (6 of 794 or 0·75%) and the hospital population (0·72%), although the incidence was 2·7% (3 of 112) in patients with early-onset pre-eclampsia with proteinuria.

Pre-eclampsia and Hypoglycæmia

Analysis of results with regard to hypoglycæmia showed two statistically significant trends in patients with pre-eclampsia. The first was an increase in the incidence of hypoglycæmia in patients with early-onset disease associated with proteinuria. In this group the incidence was 22·3% compared with 14·8% for the hospital population (table III) ($P<0.05$). This tendency towards hypoglycæmia in patients with early-onset

TABLE II—ASSOCIATION OF PRE-ECLAMPSIA AND HYPERGLYCAEMIA ACCORDING TO TIME OF ONSET AND SEVERITY OF DISEASE

—	Proteinuria		No proteinuria		Total	
	No.	%	No.	%	No.	%
Early onset pre-eclampsia (<37 wk):						
Primiparæ with pre-eclampsia	73		46		119	
Primiparæ with hyperglycæmia	14	19·2*	5	10·9 N.S.	19	16·0
Multiparæ with pre-eclampsia	39		31		70	
Multiparæ with hyperglycæmia	10	25·6†	4	12·9 N.S.	14	20·0
All patients with pre-eclampsia	112		77		189	
All patients with hyperglycæmia	24	21·4†	9	11·7 N.S.	33	17·5
Late onset pre-eclampsia (37 wk +):						
Primiparæ with pre-eclampsia	187		230		417	
Primiparæ with hyperglycæmia	25	13·4 N.S.	22	9·6 N.S.	47	11·3
Multiparæ with pre-eclampsia	48		140		188	
Multiparæ with hyperglycæmia	4	8·3 N.S.	25	17·9*	29	15·4
All patients with pre-eclampsia	235		370		605	
All patients with hyperglycæmia	29	12·3 N.S.	47	12·7 N.S.	76	12·6

*$P<0.05$; †$P<0.01$; N.S.=not significant; hospital incidence of hyperglycæmia=11·7%.[3]

TABLE III—ASSOCIATION OF PRE-ECLAMPSIA AND HYPOGLYCAEMIA ACCORDING TO TIME OF ONSET AND SEVERITY OF DISEASE

—	Proteinuria		No proteinuria		Total	
	No.	%	No.	%	No.	%
Early onset pre-eclampsia (<37 wk):						
Primiparæ with pre-eclampsia	73		46		119	
Primiparæ with hypoglycæmia	17	23·3*	8	17·4 N.S.	25	21·0
Multiparæ with pre-eclampsia	39		31		70	
Multiparæ with hypoglycæmia	8	20·5 N.S.	2	6·5 N.S.	10	14·3
All patients with pre-eclampsia	112		77		189	
All patients with hypoglycæmia	25	22·3*	10	13·0 N.S.	35	18·5
Late onset pre-eclampsia (37 wk +):						
Primiparæ with pre-eclampsia	189		230		417	
Primiparæ with hypoglycæmia	23	12·3 N.S.	24	10·4 N.S.	47	11·3
Multiparæ with pre-eclampsia	48		140		188	
Multiparæ with hypoglycæmia	9	18·8 N.S.	10	7·1*	19	10·1
All patients with pre-eclampsia	235		370		605	
All patients with hypoglycæmia	32	13·6 N.S.	34	9·2†	66	10·9

*$P<0.05$; †$P<0.01$; N.S.=not significant; hospital incidence of hypoglycæmia=14·8%.[3]

TABLE IV—CORRELATION BETWEEN GLUCOSE TOLERANCE, LOW OESTRIOL EXCRETION, AND FETAL RESULTS IN PATIENTS WITH PRE-ECLAMPSIA

Glucose tolerance	No. of patients	Œstriol assay not done	Low œstriol excretion		Small for dates infants		Apgar <5		Stillbirths	Neonatal deaths	Perinatal mortality	
			No.	%	No.	%	No.	%			No.	%
Hypoglycæmia	101	3	26	26·5†	17	16·8†	19	18·8†	4	0	4	4·0*
Hyperglycæmia	109	5	19	18·3 N.S.	5	4·6 N.S.	11	10·1 N.S.	1	0	1	0·9 N.S.
Normoglycæmia	584	7	91	15·8	51	8·7	65	11·1	4	2	6	1·0
Total	794	15	136	17·5	73	9·2	95	12·0	9	2	11	1·4

* $P<0.05$; † $P<0.01$; N.S.=not significant.

severe pre-eclampsia was more marked in primiparæ (23·3%) than in multiparæ (20·5%).

The second significant finding was a decrease in the incidence of hypoglycæmia in patients with late-onset pre-eclampsia without proteinuria. In this group the incidence was 9·2% compared with 14·8% for the hospital population (table III) ($P<0·01$).

Pre-eclampsia, Glucose Tolerance, and Fetal Hazard

The correlations between fetal hazard (low maternal œstriol excretion, infant small for dates, low Apgar score, and perinatal mortality) and abnormal glucose tolerance in the study group of 794 patients with pre-eclampsia are shown in table IV. There were statistically significant differences in the incidences of low maternal urinary œstriol excretion (26·5%), fetal growth retardation (16·8%), neonatal asphyxia (18·8%), and perinatal mortality (4·0%) in pre-eclamptic patients with hypoglycæmia compared with pre-eclamptic patients with normoglycæmia. This suggests that in patients with pre-eclampsia, hypoglycæmia is directly related to the cause of perinatal death.

In this series there was no increased risk to the fetus, according to the above parameters, in pre-eclamptic patients with hyperglycæmia. Indeed, in this group, the incidence of fetal growth retardation (4·6%) was only half that of the pre-eclamptic patients who had normal glucose tolerance (8·7%) (table IV).

Discussion

This investigation showed that there was a higher than expected incidence of hypoglycæmia in women destined to become pre-eclamptic. This, together with the positive correlation between hypoglycæmia and fetal growth retardation, suggested that a cause of pre-eclampsia may be reduced maternal supply of nutriments to the fetus. This would fit the clinical observation that fetal growth retardation often precedes the appearance of the signs of pre-eclampsia. Pre-eclampsia in association with hypoglycæmia had an ominous significance with regard to fetal outcome, the incidences of low œstriol excretion, fetal growth retardation, low Apgar score, and perinatal mortality all being higher than the incidences in those pre-eclamptic pregnancies associated with either normoglycæmia or hyperglycæmia. Abnormal carbohydrate metabolism in its widest sense substantially increases the likelihood of severe pre-eclampsia and, in the case of hypoglycæmia, materially prejudices fetal outcome.

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KIDNEY TRANSPLANTABILITY ACROSS A POSITIVE CROSS-MATCH

Cross-match Assays and Distribution of B Lymphocytes in Donor Tissues

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Summary Lymphocyte subpopulations were determined in peripheral blood, abdominal lymph-nodes, and spleens from renal allograft donors. Percentages of B lymphocytes were low in peripheral blood (mean±S.E.,10·0±1·0%), variable in lymph-nodes (28·8±3·8), and high in spleens (41·4±2·1). Microlymphocytotoxicity cross-match assays in which sera with B-cell-specific antibody were used were invariably negative with peripheral-blood lymphocytes but positive with lymph-node or spleen preparations. Four renal allografts were transplanted when the standard cross-match was positive with spleen or lymph-node but negative with blood. No hyperacute or accelerated rejection was observed. Potential recipients are often denied allografts because of a positive cross-match with either lymph-node or splenic preparations, and this could be avoided in some cases if cross-matches were performed on peripheral blood or B-lymphocyte-depleted splenic or lymph-node preparations. These results accord with those of other workers who found that B-cell pre-sensitisation is not a contraindication to transplantation.

Introduction

ALLOGRAFT transplantation is generally not performed when donor-specific lymphocytotoxins are present in the recipient (positive cross-match), because this greatly increases the risk of hyperacute and accelerated graft failures.[1–3] Two main types of lymphocytotoxins have been described: (i) those active against HLA antigens present on most lymphocytes, and (ii) those active against non-HLA antigens present mainly on B lymphocytes.[4–6] Standard cytotoxicity assays in which peripheral-blood lymphocytes are used usually fail to detect these B-cell-specific lymphocytotoxins, mainly because B lymphocytes are present in small numbers. Thus in some cases allograft transplants are being done in the presence of B-cell-specific antibodies. Ettenger et al. evaluated the role of B-cell-specific lymphocytotoxins in graft survival in a prospective trial.[7] As usual transplants were performed only when the conventional complement-dependent microlymphocytotoxicity assay (standard cross-match) was negative. B-cell-specific antibodies were determined by performing the same cross-match assay on T-cell-depleted lymphocyte preparations (B-cell-positive cross-match). All of their 7 recipients with pre-formed donor-specific B-lymphocyte antibodies had functioning allografts 1–6 months post transplant.

Before a policy of not transplanting in the presence of lymphocytotoxins was generally adopted by transplant centres, it was observed that 30% of allografts transplanted across a positive standard cross-match did not undergo hypercute or accelerated rejection.[8] This interesting observation and the favourable outcome of graft survival in recipients with a B-cell-positive cross-match