PAPERS AND SHORT REPORTS

Glycaemic control in diabetic nephropathy

J J BENDING, J C PICKUP, G C VIBERTI, H KEEN

Abstract

To investigate the quality of glycaemic control that is achievable in diabetic patients with persistent proteinuria and asymptomatic but declining renal function three matched groups of patients were studied. The first comprised diabetics with proteinuria receiving continuous subcutaneous insulin infusion; the second, diabetics without proteinuria receiving continuous subcutaneous insulin infusion; and the third, diabetics with proteinuria receiving conventional insulin treatment. Glycaemic control in patients receiving continuous subcutaneous insulin infusion was shown to be appreciably worse during the daytime in diabetics with proteinuria than in diabetics without proteinuria, although greatly superior to that in diabetics with proteinuria receiving conventional insulin treatment. The loss of glycaemic control in patients with proteinuria receiving continuous subcutaneous insulin infusion probably occurred as a response to daytime hypoglycaemia and a consequent reduction in the proportion of the total insulin dose given prandially.

Difficulty in controlling blood glucose concentrations may be a factor in the failure of intensified insulin regimens to influence the progression of diabetic renal disease.

Introduction

The ability to achieve and maintain strict glycaemic control in diabetic patients with persistent proteinuria and renal

dysfunction is important because correcting abnormalities in metabolic control may slow the development of microangiopathy. Continuous subcutaneous insulin infusion can provide long periods of nearly normal glycaemia in insulin dependent diabetics without renal impairment, and in diabetics with early functional abnormalities of the kidney (testing with Albustix for microalbuminuria yields negative results) it rapidly reduces urinary rates of excretion of albumin and may return them to normal.¹ In 1983 we showed, however, that in a small group of diabetics with more advanced nephropathy (testing with Albustix for proteinuria yields persistently positive results) up to two years of continuous subcutaneous insulin infusion did not appreciably slow the decline in the glomerular filtration rate or reduce either proteinuria or the rate of rise in plasma creatinine concentrations.² Although glycaemic control was appreciably better with continuous subcutaneous infusion of insulin than with conventional insulin treatment, failure to influence the progression of nephropathy may have resulted, at least in part, from difficulty in achieving the same degree of strict control as in diabetics who do not have proteinuria and are treated with continuous subcutaneous insulin infusion.

Renal failure also has complex metabolic consequences. Insulin metabolism is altered, and daily requirements may fall considerably in diabetics treated with insulin. Moreover, patients with renal failure but without diabetes may develop intolerance of glucose *de novo*,³⁻⁵ mainly, but not exclusively, because of an increased resistance of tissue to the effects of insulin of "post receptor" origin.⁶ Although the management of patients with renal failure but previously without diabetes has recently been reviewed,⁷ little attention has been given to the quality of glycaemic control that is now possible in diabetics with proteinuria but only mild renal impairment.

These reasons for suspecting difficulty in achieving strict glycaemic control in proteinuric diabetics during optimised regimens such as continuous subcutaneous insulin infusion led us to measure such derangements by measuring a number of variables of control in three groups of patients. We therefore compared the quality of glycaemic control achieved with continuous subcutaneous insulin infusion in diabetics with and without proteinuria and with conventional insulin treatment in diabetics with proteinuria.

Unit for Metabolic Medicine, Guy's Hospital Medical School, London SE1 9RT

J J BENDING, MRCP, research honorary senior registrar
G C VIBERTI, MD, senior lecturer grade research fellow
H KEEN, FRCP, professor of human metabolism

Department of Chemical Pathology, Guy's Hospital Medical School, London

J C PICKUP, BM, DPHIL, senior lecturer and honorary consultant

Patients and methods

CHARACTERISTICS OF PATIENTS

Table I shows the clinical characteristics of the three groups of patients studied. Group 1 comprised six insulin dependent diabetics with established diabetic nephropathy and persistent proteinuria (as shown by testing with Albustix) being treated with continuous subcutaneous infusion of insulin; group 2 comprised six insulin dependent diabetics with no evidence of diabetic nephropathy (repeatedly negative results on Albustix testing for proteinuria and normal plasma creatinine concentrations and glomerular filtration rates), being treated with continuous subcutaneous infusion of insulin; and group 3 comprised six patients with established diabetic nephropathy and persistent proteinuria who were all receiving twice daily injections of insulin. The groups were matched for age, sex, and duration of diabetes; in all patients plasma C peptide concentrations were below 0.2 nmol/l six minutes after administration of 1 mg glucagon intravenously.⁸ The patients were studied for 12 to 30 months from 1981 to 1983.

In patients with nephropathy, non-diabetic causes of renal damage were excluded on clinical and biochemical grounds (confirmed in three patients (cases 3, 4, and 16) by histological findings after renal biopsy). None of the patients with nephropathy had symptoms from their renal failure, and in particular none had reached the stage of nausea and vomiting; their appetites were normal.

Table II shows the known duration of proteinuria and the mean glomerular filtration rate during the study (five measurements were taken at intervals of three to six months) in patients in groups 1 and 3. The mean duration of persistent proteinuria was significantly longer in patients receiving continuous subcutaneous insulin infusion than in those receiving conventional insulin treatment. The difference in mean glomerular filtration rate between the two groups did not reach significance; one patient in group 3 still had a raised but declining glomerular filtration rate after more than three years' proteinuria.

No special advice on diet had been given to the patients with proteinuria, and dietary assessment showed no significant difference between the groups in mean dietary intake of energy or in the proportions of protein, fat, and carbohydrate in their diets. Furthermore, there was no significant difference in mean body mass index between the patients in groups 1 and 3 during the study. Seven of the 12 patients with diabetic nephropathy (four patients in group 1 and three in group 3) were receiving diuretics and β sympathetic blocking agents because of hypertension, in addition to their insulin.

All 12 patients with proteinuria had autonomic neuropathy as assessed by postural hypotension, pulse rate on standing, hand grip, beat to beat variation with respiration, heat induced sweat test, and Valsalva's ratio. The six patients who did not have proteinuria did not have autonomic neuropathy (absence of postural hypotension and normal response of pulse rate to standing).

PROTOCOL

Patients were admitted for study to a metabolic ward for five periods of 24 hours each at intervals of three to six months over one to two and a half years. They were fully ambulant during the day and continued with their normal diets during each admission. Continuous subcutaneous infusion of insulin was performed as previously described with a Mill Hill infuser model 1001 HM (Muirhead

Medical).⁹ Venous blood was withdrawn every two hours via an indwelling Teflon cannula for measurement of plasma glucose concentrations by an automatic analyser (glucose oxidase method, Yellow Springs Instrument Co). Five such profiles were recorded for each patient. The variables of glycaemic control which were calculated in each patient were taken as the mean, standard deviation, mean daily range, and M value. The M value was derived from the formula:

$$M = \frac{\sum \left| 10 \log_{10} \frac{PG}{4.44} \right|^3}{n}$$

where PG = each of n plasma glucose concentrations (mmol/l) and n = number of samples.^{10 11}

TABLE II—Glomerular filtration rate (GFR) and duration of persistent proteinuria in diabetics with renal dysfunction receiving either continuous subcutaneous insulin infusion (group 1) or conventional insulin treatment (group 3)

Case No	Duration of proteinuria (years)	Mean GFR during study period (ml/min/1.73 m ²)
Group 1		
1	>4	77.2
2	>4	33.0
3	>10	13.9
4	>10	24.9
5	6	36.7
6	8	21.6
Mean	>7*	34.5†
Group 3		
13	1	84.7
14	3	43.8
15	3	177.6
16	3	10.0
17	2	41.3
18	4	65.9
Mean	2.7*	70.5†

Group 1 v group 3: *p<0.005, †NS.

Patients treated with continuous subcutaneous insulin infusion also estimated fasting capillary blood glucose concentrations with Dextrostix (Ames) on 10 consecutive days at home, at a randomly selected time during the period of study. The mean (SD) of these 10 recordings was estimated in each patient as a measure of day to day variability of basal (fasting) control of glycaemia.

The incidence of biochemical hypoglycaemia was determined in each of the three groups by calculating the proportion of all plasma glucose concentrations that were lower than an arbitrary value of 3.0 mmol/l (54 mg/100 ml) during the 24 hour periods in hospital. Glomerular filtration rate was estimated after a single injection of disodium edetate labelled with chromium-51¹² and corrected for body surface area. Differences within and between means for each group were tested for significance by Student's paired or unpaired t test, on log transformed data if necessary. The study was approved by the Guy's Hospital ethical committee.

TABLE I—Clinical characteristics of diabetics with proteinuria receiving continuous subcutaneous insulin infusion (group 1), diabetics receiving the same treatment but without proteinuria (group 2), and diabetics with proteinuria receiving conventional insulin treatment (group 3)

Group 1							Group 2							Group 3						
Case No	Sex	Age (years)	Duration of diabetes (years)	Daily insulin dose (U/kg)			Case No	Sex	Age (years)	Duration of diabetes (years)	Daily insulin dose (U/kg)			Case No	Sex	Age (years)	Duration of diabetes (years)	Daily insulin dose		
				Basal	Prandial	Total					Basal	Prandial	Total					Type and No of units*	Total U/kg/day	
1	M	62	31	0.40	0.20	0.60	7	M	55	27	0.17	0.12	0.29	13	M	57	30	Mixtard 26, 16	0.50	
2	M	63	18	0.30	0.20	0.49	8	M	60	26	0.41	0.27	0.67	14	M	61	20	{ Actrapid 10, 10 Monotard 24, 20 }	0.76	
3	F	37	30	0.32	0.06	0.37	9	F	49	15	0.48	0.34	0.82	15	F	38	17	{ Soluble 16, 12 Isophane 16, 16 }	0.98	
4	F	37	23	0.22	0.08	0.30	10	F	42	18	0.38	0.28	0.67	16	F	47	17	{ Actrapid 8, 2 Monotard 10, 12 }	0.48	
5	M	60	18	0.55	0.30	0.85	11	M	52	26	0.34	0.24	0.58	17	M	59	18	{ Actrapid 8, 12 Monotard 16, 20 }	0.67	
6	M	49	33	0.33	0.10	0.43	12	M	46	27	0.38	0.31	0.70	18	M	52	22	{ Actrapid 16, 12 Monotard 8, 8 }	0.60	
Mean		51.3	25.5						50.6	23.2						52.3	20.7			

*Two dosages, as insulin was given twice daily.

Results

GLYCAEMIC CONTROL

Table III shows the variables of glycaemic control in the three groups of patients. The mean daily plasma glucose concentration in patients receiving continuous subcutaneous insulin infusion was significantly higher in those with proteinuria (group 1) than in those without (group 2) ($p < 0.001$), although the mean plasma glucose concentration in patients in group 1 was still significantly lower ($p < 0.02$) than that in patients with proteinuria receiving conventional insulin treatment (group 3).

TABLE III—Control of glycaemia achieved in diabetics with proteinuria receiving continuous subcutaneous insulin infusion (group 1), in diabetics without proteinuria receiving continuous subcutaneous insulin infusion (group 2), and in diabetics with proteinuria receiving conventional insulin treatment (group 3)

	Mean plasma glucose* (mmol/l)	Mean daily SD plasma glucose† (mmol/l)	Mean M value (mmol/l)	Plasma glucose range‡ (mmol/l)	Mean day to day variability§	Mean % glucose < 3.0 mmol/l
Group 1	7.78	3.71	34.3	51.7	1.9	4.9
Group 2	5.99	2.44	14.0	33.7	1.3	10.7
Group 3	11.43	5.97	105.0	88.2		1.7

Significance:

Group 1 $\bar{x}$ group 2	< 0.001	0.01	< 0.001	< 0.01	NS	< 0.05
Group 2 $\bar{x}$ group 3	< 0.01	0.01	< 0.01	< 0.01		< 0.01
Group 1 $\bar{x}$ group 3	< 0.02	NS	< 0.05	< 0.05		< 0.05

* Calculated as the mean of the daily mean plasma glucose concentrations for the patients within the group.

† Calculated as the mean of the daily standard deviations for the patients in the group.

‡ Sum of highest minus lowest value during each of five 24 hour profiles.

§ Standard deviation of the mean fasting blood glucose concentrations on 10 consecutive days.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

The standard deviation and range of plasma glucose concentrations, used to estimate dispersion of values throughout the day, were also significantly greater ($p < 0.01$) in patients in group 1 than in those in group 2, but the greatest variability was in the diabetics with proteinuria who were receiving conventional insulin treatment. The mean M value (table III) in group 1 was significantly higher ($p < 0.001$) than that in group 2 but significantly lower ($p < 0.05$) than that in group 3.

A trend towards greater day to day variability in patients in group 1 compared with patients in group 2 was shown by the standard deviations of 10 consecutive fasting blood glucose concentrations, but this difference did not reach significance.

The proportion of plasma glucose concentrations below 3.0 mmol/l was significantly smaller in patients in group 1 than in those in group 2 ($p < 0.05$). The smallest proportion was recorded in the diabetics with proteinuria receiving conventional insulin treatment (group 3).

Figure 1 shows the mean circadian plasma glucose concentrations

FIG 1—Mean (SD) circadian plasma glucose concentrations in diabetics with proteinuria receiving conventional insulin injection (—○—), diabetics without proteinuria receiving continuous subcutaneous insulin infusion (---●---), and diabetics with proteinuria and receiving continuous subcutaneous insulin infusion (· · · □ · · ·).

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

for each of the three groups. Fasting values in groups 1 and 2 were similar, but during the day the concentrations were higher in those with proteinuria (group 1), these differences reaching significance at 1200 ($p < 0.02$) and 1800 ($p < 0.01$). Values in patients receiving conventional insulin treatment were higher than those in the two other groups at most times during the 24 hours but particularly during waking hours.

DOSAGES OF INSULIN

Table IV shows the mean daily doses of insulin in the three groups of patients one year after diagnosis and when last seen (14–32 years later). The dose of insulin was significantly reduced over this time in the patients with proteinuria (by 30% in group 1 ($p < 0.05$) and by 22% in group 3 ($p < 0.005$)) but not in the diabetics without proteinuria. Review of the patients' history of insulin dosage showed that the reduction in dosage had begun shortly after the onset of persistent proteinuria.

TABLE IV—Mean (SD) insulin dosages (U) in the three groups of patients one year after diagnosis and when last seen (14 to 32 years later)

	One year after diagnosis	When last seen	p
Group 1	55 (23)	35 (18)	< 0.05
Group 2	49 (8.6)	51 (17)	NS
Group 3	62 (17)	45 (14.5)	< 0.005

Table I lists the insulin doses being received by each patient at the end of the study. The mean total daily dose of insulin was slightly, but not significantly, lower in patients in group 1 than in those in group 2 (0.51 (0.19) v 0.62 (0.18) U/kg). When the prandial dose was expressed as a proportion of the total dose, however, it was significantly smaller in patients in group 1 than group 2 (33.0 (4.18)% v 41.8 (1.33)% ($p < 0.001$)). Figure 2 shows the changes throughout the study in the proportion of the total insulin dose given prandially in groups 1 and 2. The prandial dose was significantly reduced ($p < 0.05$) during the first week in patients in group 1 in response to initial symptomatic diurnal hypoglycaemia that was either recorded in hospital or reported by the patients at home. No such hypoglycaemia was experienced by the patients without proteinuria.

FIG 2—Comparison of mean (SD) prandial insulin dosage (% of total dose) during 25 months of study in two groups of diabetics, one with proteinuria (—●—) the other without (---○---), receiving continuous subcutaneous insulin infusion.

Discussion

The results of this study indicate that strict glycaemic control with continuous subcutaneous infusion of insulin in diabetic patients is more difficult to achieve in those who have proteinuria than in those who do not, the mean daily plasma glucose concentration and variation around the daily mean being

higher in patients with proteinuria. Nevertheless, control with continuous subcutaneous infusion in patients with proteinuria was greatly superior to that achieved in a matched group of diabetics with proteinuria receiving conventional insulin treatment.

The observation that glycaemic control induced by continuous subcutaneous insulin infusion was less "tight" is associated with the finding that the ratio of prandial to total insulin dose in these patients was significantly lower ($p < 0.001$) than in the group of patients without proteinuria receiving continuous subcutaneous insulin infusion. This would explain the largely diurnal loss of control in patients with proteinuria that occurred within the first week of treatment with continuous infusion. The insulin dosage was adjusted at that time in response to daytime symptomatic hypoglycaemia, reported in each patient in the group. We do not know whether hypoglycaemia developed in patients with proteinuria because of accompanying autonomic neuropathy or because of therapeutic adrenergic receptor blockade, or both, but we had noted that the patients without proteinuria did not appear to have autonomic neuropathy.

Difficulty in achieving strict glycaemic control in patients with proteinuria, even during intensified insulin regimens, might be expected for several reasons. Firstly, intolerance of carbohydrates, which may develop de novo with advancing renal failure in patients previously not suffering from diabetes,³⁻⁵ may add to the difficulty of achieving nearly normal glucose concentrations in diabetics with renal disease. Peripheral resistance to the effects of insulin appears to be a major factor in the development of this intolerance of glucose and may be largely accounted for by an accompanying defect in postreceptor binding.⁶ Other mechanisms may also contribute.¹³⁻¹⁵

Secondly, loss of insulin removal by the kidneys with advancing kidney disease^{16, 17} probably chiefly accounts for the increased plasma concentrations of insulin in patients with renal failure who do not have diabetes^{18, 19} and may also account for diminishing exogenous requirements in diabetics with advancing renal disease.^{16, 20-25} We confirmed the second of these observations in both of our groups of patients with proteinuria: insulin doses were significantly smaller in both groups at the time of the present study than at one year after diagnosis. The fall in dose is unlikely to have been due to the change from conventional insulin treatment to continuous subcutaneous insulin infusion as no such fall was found (over a mean period of 23 years) in the patients who did not have proteinuria despite their having changed to treatment with continuous subcutaneous insulin infusion between one and two and a half years before the study. In addition, the fall in daily dosages of insulin is also unlikely to have been due to a change from traditional beef insulin to highly purified pork insulin at some stage during the period of treatment. Six of the 12 patients with proteinuria had been treated with highly purified porcine insulin from diagnosis, and one had continued to receive beef insulin of conventional purity. In the patients whose treatment had been changed to highly purified porcine insulin the reduction in dosage of insulin was not temporally related to the change and occurred at a later date, presumably with the onset and progression of nephropathy.

End stage renal failure with accompanying weight loss, debilitation, nausea, and vomiting will clearly contribute to disturbed metabolic control in diabetics, probably as a response to restricted intake of energy. Even patients maintained on adequate nutritional programmes, however, manifest intolerance of carbohydrate in chronic renal failure.^{26, 27} Our patients with proteinuria had not developed symptomatic uraemia, did not complain of anorexia, and consumed diets that did not differ appreciably in total content of energy or in composition from those consumed by the patients without proteinuria.

Patients with renal impairment were selected on the basis that Albustix testing for proteinuria yielded persistently positive results. One such patient, who was receiving conventional insulin treatment, had a mean glomerular filtration rate during the study that was still above the normal range even though she

had had proteinuria with a falling glomerular filtration rate for three years. The mean glomerular filtration rate was higher and the duration of known proteinuria appreciably shorter in diabetics with proteinuria receiving conventional insulin treatment than in diabetics with proteinuria receiving continuous subcutaneous insulin infusion. Assuming that nephropathy associated with a low glomerular filtration rate makes control of glycaemia more difficult, this underlines the differences in the ability of the two treatments to control glycaemia.

We conclude that relaxing the administration of prandial insulin in response to diurnal hypoglycaemia accounts for the loss of glycaemic control in diabetics with proteinuria. This does not prove that strict near normoglycaemia is impossible to achieve in these patients (for example, by finer tuning of prandial insulin boosts), but it would appear to support the advice that continuous subcutaneous infusion of insulin (or indeed any rigorous intensification of insulin treatment) should be approached with care in diabetic patients who have lost hormonal counterregulation and show warning symptoms of hypoglycaemia.²⁸ This loss of diurnal glycaemic control in diabetics with proteinuria treated with continuous subcutaneous insulin infusion may partly explain the failure of this technique to influence the progression of nephropathy.² In the search for strict metabolic correction of diabetes in advancing clinical nephropathy, its long term effectiveness in influencing the progression of the disease must be balanced against the risks of hypoglycaemia developing.

We thank the sisters and staff nurses of the Peter Bishop metabolic ward for their help, Ms Rosemary Hunt for help with the dietary assessments, and Mrs Jean Gray for secretarial help.

References

- Viberti GC, Pickup JC, Jarrett RJ, Keen H. Effect of control of blood glucose on urinary excretion of albumin and B₂-microglobulin in insulin-dependent diabetes. *N Engl J Med* 1979;300:638-41.
- Viberti GC, Bilous RW, MacKintosh D, Bending JJ, Keen H. Long term correction of hyperglycaemia and progression of renal failure in insulin dependent diabetes. *Br Med J* 1983;286:598-602.
- Linder GC, Hiller A, Van Slyke DD. Carbohydrate metabolism in nephritis. *J Clin Invest* 1925;1:247-72.
- Horton ES, Johnson C, Lebovitz HE. Carbohydrate metabolism in uremia. *Ann Intern Med* 1968;68:63-74.
- Spitz IM, Rubenstein AH, Bersohn I, Abrahams C, Lowy C. Carbohydrate metabolism in renal disease. *Q J Med* 1970;39:201-6.
- Smith D, DeFronzo RA. Insulin resistance in uraemia mediated by post-binding defects. *Kidney Int* 1982;22:54-62.
- Amico JA, Klein I. Diabetic management in patients with renal failure. *Diabetes Care* 1981;4:430-4.
- Faber OK, Binder C. C-peptide response to glucagon. A test for the residual β -cell function in diabetes mellitus. *Diabetes* 1977;26:605-10.
- Pickup JC, Keen H, Viberti GC, et al. Continuous subcutaneous insulin infusion in the treatment of diabetes mellitus. *Diabetes Care* 1980;3:290-300.
- Schlichtkrull J, Munck O, Jersild M. The M-value, an index of blood-sugar control in diabetes. *Acta Med Scand* 1965;177:95-102.
- Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 1970;19:644-55.
- Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by single injection method using ⁵¹Cr-EDTA. *Clin Sci* 1969;37:169-80.
- Sherwin RS, Basti C, Finkelstein FO, et al. Influence of uremia and hemodialysis on the turnover and metabolic effects of glucagon. *J Clin Invest* 1976;57:722-31.
- Garber AJ. Skeletal muscle protein and amino acid metabolism in experimental chronic uremia in the rat. Accelerated alanine and glutamine formation and release. *J Clin Invest* 1978;62:623-32.
- Harter HR, Karl IE, Klahr S, Kipnis DM. Effects of reduced renal mass and dietary protein intake on amino acid release and glucose uptake by rat muscle in vitro. *J Clin Invest* 1979;64:513-23.
- Rubenstein AH, Spitz I. Role of the kidney in insulin metabolism and excretion. *Diabetes* 1968;17:161-9.
- Chamberlain MJ, Stummler L. The renal handling of insulin. *J Clin Invest* 1967;46:911-9.
- Rabkin R, Simon NM, Steiner S, Colwell JA. Effect of renal disease on renal uptake and excretion in man. *N Engl J Med* 1970;282:182-7.
- Jaspan JB, Mako ME, Kuzuya H, Blix P, Horwitz DL, Rubenstein AH. Abnormalities in circulating beta cell peptide in chronic renal failure:

- comparison of C-peptide, pro-insulin and insulin. *J Clin Endocrinol Metab* 1977;**45**:441-5.
- ²⁰ Zubrod CG, Eversole SL, Dana GW. Amelioration of diabetes and striking rarity of acidosis in patients with Kimmelstiel-Wilson lesions. *N Engl J Med* 1951;**245**:518-25.
- ²¹ Runyan JW, Hurwitz D, Robbins SL. Effect of Kimmelstiel-Wilson syndrome on insulin requirements in diabetes. *N Engl J Med* 1955;**252**:388-91.
- ²² Epstein FH, Zupa VJ. Clinical correlates of the Kimmelstiel-Wilson lesion. *N Engl J Med* 1956;**254**:896-900.
- ²³ Kalliomäki JL, Markkanen TK, Sourander LB. Correlation between insulin requirement and renal retention in diabetic nephropathy. *Acta Med Scand* 1960;**166**:423-4.
- ²⁴ Hatch FE, Parrish AE. Apparent remission of a severe diabetic on

- developing the Kimmelstiel-Wilson syndrome. *Ann Intern Med* 1961;**54**:544-9.
- ²⁵ Thomsen AC. *The kidney in diabetes mellitus*. Copenhagen: Munksgaard, 1965:220.
- ²⁶ Hampers CL, Soeldner JS, Doak PB, Merrill JP. Effect of chronic renal failure and haemodialysis on carbohydrate metabolism. *J Clin Invest* 1966;**45**:1719-31.
- ²⁷ Lowrie EG, Soeldner JS, Hampers CL, Merrill JP. Glucose metabolism and insulin secretion in uremic, prediabetic, and normal subjects. *J Lab Clin Med* 1970;**76**:603-15.
- ²⁸ Unger R. Meticulous control of diabetes: benefits, risks, and precautions. *Diabetes* 1982;**31**:479-83.

(Accepted 31 January 1984)

Psychosocial stress in pregnancy and its relation to low birth weight

RICHARD W NEWTON, LINDA P HUNT

Abstract

The relation of low birth weight to psychosocial stress in pregnancy was examined using a life events inventory and a state anxiety index. Two hundred and fifty women were randomly selected and interviewed three times during pregnancy and shortly after delivery. Twenty six were excluded. Of the remaining 224 women, nine miscarried, 195 had healthy term babies, and 20 gave birth to babies that were either premature or of low birth weight at term.

Low birth weight and prematurity were significantly associated with objective major life events but not state anxiety. The occurrence of objective major life events in the third trimester may be important in precipitating preterm labour. Cigarette smoking was the best predictor and objective major life events the second best predictor of low birth weight. The result was not dependent on social class.

These findings suggest that cigarette smoking may be an important mediator of stress on the fetus. Antenatal care should take greater account of stress in pregnancy, and social support systems should be evaluated.

Introduction

Previous work on stress in pregnancy has often incorporated serious methodological errors. Maternal factors as diverse as a marginal placenta and pre-eclampsia and infant factors as diverse as jaundice and cord around the neck have been used to define adverse outcome of pregnancy.¹ In one study infant abnormalities ranged from hydrocephalus to a bruised nose.² This failure to categorise abnormality prevents sensible inter-

pretation of the results. Studies have also generally failed to consider the importance of psychosocial stress relative to factors known to be associated with low birth weight, such as social class and cigarette smoking, though there have been notable exceptions.³ Retrospective studies have often allowed the possible bias of results by "effort after meaning," a term that implies that women experiencing an adverse outcome of pregnancy may make a conscious effort to explain this by blaming a particular life event that has happened to them.

Because of these methodological problems in previous studies we carried out a prospective study of an unselected population of women who were interviewed at least twice during pregnancy by a single interviewer (RWN). The number, nature, and subjective effect of any life events were recorded, the outcome of pregnancy defined, and the contribution of social class and cigarette smoking considered. We report here our results.

Patients and methods

The study population was randomly selected from women booking into St Mary's Hospital, Manchester, for their antenatal care. Hospital Activity Analysis showed that 86% of babies of low birth weight were booked deliveries. To avoid language difficulties only women born in the United Kingdom were interviewed, irrespective of racial origin; 95% were white.

Assuming a prevalence of babies of low birth weight of 8-10% and a prevalence of major life events similar to that recorded in our previous, retrospective study,⁴ we selected a population of 250 to give a group of about 20 babies of low birth weight (≤ 2500 g) and, probably, a significant result.

Patients were interviewed at their initial booking visit, at about 30 weeks' gestation, when possible between 37 and 40 weeks' gestation, and shortly after delivery. Age, marital state, husband's occupation, number of people per room (as defined by the Office of Population Censuses and Surveys⁵) at home, obstetric history, and smoking habit were recorded. The modified life events inventory used in the retrospective study⁴ was presented at each interview and the experience and timing of any life event during pregnancy noted. Patients were also asked to complete Spielberger's state anxiety index⁶ according to how they felt "at that moment in the antenatal clinic"; they also completed the index in relation to any major life event experienced according to how they had "felt about it at the time."

The state anxiety index is self administered and contains 20 items, each scored on a scale of 1 to 4. The four categories are: 1, not at all; 2, somewhat; 3, moderately so; and 4, very much so. Half of the

Booth Hall Children's Hospital, Manchester M9 2AA
RICHARD W NEWTON, MD, MRCP, consultant paediatric neurologist

Stopford Building, University of Manchester, Manchester 13
LINDA P HUNT, MSC, MIS, lecturer, faculty of medicine computational group

Correspondence to: Dr R W Newton.