Prolactin in Hypertensive Pregnancy

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Summary

Plasma prolactin levels were measured in 68 pregnant women with hypertension at 32 weeks gestation. They were raised in pregnancies with pre-eclamptic features, most significantly in women with a rising plasma urate level. No correlation was found between the level of the untreated blood pressure and prolactin. Proteinuria did not influence prolactin levels independently of changes in the plasma urate. The differences in prolactin levels could not be ascribed to the drugs administered.

Introduction

Pre-eclampsia is characterized by hypertension with increased vascular reactivity (Gant *et al.*, 1973), fluid retention, and impaired renal function usually associated with proteinuria. Excess circulating pressor or fluid-retaining agents related to the renin-angiotensin system (Weir *et al.*, 1973), deoxycorticosterone (Brown *et al.*, 1972), cortisol (Kopelman and Levitz, 1970), or aldosterone (Thomas and Flynn, 1964) have not been identified in pre-eclampsia.

Prolactin causes sodium and water retention in some vertebrates (Ensor and Ball, 1972) and may have comparable effects in mammals (Lockett, 1965; Horrobin *et al.*, 1971). Possibly some of the features of pre-eclampsia could be caused by prolactin (Friesen *et al.*, 1973; Horrobin *et al.*, 1973). We have therefore measured plasma prolactin levels in hypertensive pregnancies to determine whether raised values are associated with any features of pre-eclampsia. Because the drugs routinely used to treat pre-eclampsia (methyldopa, diazepam, barbiturates) may influence prolactin secretion part of this study was directed towards excluding this possibility.

Patients and Methods

EFFECT OF METHYLDOPA ON PROLACTIN LEVELS

Patients included in a trial of methyldopa for mild and moderate hypertension in pregnancy were studied at 24, 28, 32, 34, 36, and 38 weeks of gestation. They were included in the trial if on two occasions more than 24 hours apart and before 28 weeks of gestation either the systolic or diastolic pressure equalled or exceeded 140 or 90 mm Hg respectively. All blood pressures were measured with a London School of Hygiene sphygmomanometer to minimize observer bias. Patients were allocated at random to a treatment or control group.

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RELATION BETWEEN PRE-ECLAMPSIA AND PROLACTIN

Altogether 68 patients with hypertension as defined above were studied at 32 weeks of gestation; 48 were outpatients and 20 were inpatients. Thirty-four of them were taking methyldopa. All of the inpatients were sedated with diazepam, nitrazepam, amylobarbitone sodium, or phenobarbitone. None of the patients was restricted in fluid, salt, or food intake. No patient was on diuretic therapy.

CLINICAL

The patients were studied between 09·00 and 12·00 hours. Three blood pressure readings were taken, the first after five minutes' rest in the left lateral recumbent position, the second standing, and the third after one minute of gentle, standardized exercise, the mean of these being taken as the blood pressure for each patient. Oedema was graded by one observer on a scale 0-3 (absent to severe) in three sites, face, hands, and ankles. The sum of the three grades was used as an "oedema score." Venous blood was taken into lithium heparin as anticoagulant, and plasma separated within three hours of sampling; 2 ml was stored at −30°C for prolactin assay, and 5 ml was assayed for urate by routine automated methods (S.M.A. 12/60).

Hypertension, oedema, proteinuria, and a rising plasma urate level were the four features of pre-eclampsia studied. Significant oedema was defined as a score of 5 or more. Proteinuria was present if a midstream specimen of urine contained more than 0·3 g/l in the absence of infection. A rising plasma urate level was defined as an increase of 0·059 mmol/l (1 mg/100 ml) or more in the four weeks preceding the study.

LABORATORY

Plasma prolactin was measured by a specific double antibody radioimmunoassay, as described (McNeilly, 1973; McNeilly and Hagen, 1974), and the results were expressed as μg of standard human pituitary prolactin per litre. Interassay and intra-assay variation as a percentage coefficient of variation of replicate serum samples was 10% and 4% respectively.

Results

The mean plasma prolactin levels in the patients treated with methyldopa showed no significant or consistent differences from those of the untreated control group (table I). Of the 68 hypertensive women studied at 32 weeks of gestation 22 had a rising plasma urate level (table II). The prevalence of oedema was twice as high in these patients and all the cases of proteinuria were in this group. None of the 48 outpatients received any treatment other than antihypertensive therapy.

Of the 68 patients 34 were primigravid and 34 were multiparous; their mean prolactin levels were similar, 77 ± 4·6 (S.E. of mean) μg/l and 76 ± 5·3 μg/l respectively. Altogether 34 of the 68 women took no antihypertensive agents. Their mean systolic and diastolic blood pressures are shown in table III. Those with a high prolactin level, arbitrarily defined as 80 μg/l or more, had blood pressure levels identical with those of patients with a low prolactin level. Ten patients had proteinuria. They had significantly higher mean prolactin levels than the remaining 58 with no proteinuria ($P < 0.05$) (table IV). Similarly, the 12 patients with a high oedema score had higher levels of prolactin ($P < 0.05$). A much more significant difference in prolactin levels was found when the patients were classified by changes in their plasma urate levels (table V). Those with a rising urate level had a considerably higher prolactin level than those with a steady urate level ($P < 0.001$). This difference

persisted when only outpatients were considered, in whom the unknown effects of sedative drugs could be excluded.

When the patients were divided according to the behaviour of their plasma urate levels (table VI) those with a high oedema score also had higher prolactin levels. The numbers of patients were small and the differences were not significant. The 10 patients with proteinuria all had a rising urate level. Their mean prolactin levels were similar to those of the 12 patients with a rising plasma urate level and no proteinuria (table VI).

TABLE I—*Mean Plasma Prolactin Levels (μg/l) ± S.E. of Mean in Hypertensive Pregnant Women Treated with Methyldopa and in Untreated Hypertensive Pregnant Controls. Numbers of Patients are Given in Parentheses*

Weeks of Gestation	Hypertensive Controls	Hypertensive Treated Patients
24	52·7 ± 5·7 (14)	54·9 ± 4·7 (13)
28	63·1 ± 5·2 (23)	66·7 ± 4·8 (19)
32	63·4 ± 4·5 (18)	70·2 ± 5·8 (17)
34	79·5 ± 8·0 (18)	70·0 ± 3·2 (14)
36	75·3 ± 4·1 (24)	71·0 ± 3·1 (20)
38	67·4 ± 4·8 (23)	73·1 ± 4·8 (14)

TABLE II—*Details of Patients Studied at 32 Weeks of Gestation*

	No. with Rising Plasma Urate Level	No. with Steady Plasma Urate Level	Total
All patients:	22	46	68
Oedema score ⩾5	6	6	12
Proteinuria present	10	0	10
No oedema or proteinuria	10	40	50
Antihypertensive drugs:			
Methyldopa alone	7	20	27
Methyldopa + hydrallazine	5	2	7
None	10	24	34
Outpatients	8	40	48
Inpatients	14	6	20
Inpatient drugs:			
Continuous sedation	9	0	9
Nocturnal sedation	5	5	10
Antiemetic	0	1	1

TABLE III—*Untreated Women at 32 Weeks: Mean Blood Pressures ± S. E. of Mean in "High" and "Low" Prolactin Groups. Numbers of Patients are Given in Parentheses.*

	Systolic	Diastolic
Prolactin ⩾80 μg/l	129·8 ± 3·7 (15)	72·9 ± 3·1 (15)
Prolactin ⩽79 μg/l	129·1 ± 2·9 (19)	72·4 ± 2·6 (19)

TABLE IV—*Mean Plasma Prolactin Levels (μg/l) ± S.E. of Mean and Prevalence of Proteinuria and of High and Low Oedema Scores*

	Prolactin Level	No. of Patients
Proteinuria present	91·7 ± 9·8	10
Proteinuria absent	75·2 ± 3·6	58
Significance	0·025 < P < 0·05	
Oedema score ⩾5	91·3 ± 3·5	12
Oedema score ⩽4	74·7 ± 3·6	56
Significance	0·025 < P < 0·05	

TABLE V—*Mean Plasma Prolactin Levels (μg/l) ± S.E. of Mean in Patients with Rising or Steady Plasma Urate Levels*

	Prolactin Level	No. of Patients
All patients:		
Rising plasma urate	93·8 ± 7·4	22
Steady plasma urate	70·0 ± 3·1	46
Significance	P < 0·001	
Outpatients:		
Rising plasma urate	103·0 ± 15·8	8
Steady plasma urate	68·3 ± 3·5	40
Significance	P < 0·005	

TABLE VI—*Relation between Mean Plasma Prolactin Levels (μg/l) ± S.E. of Mean and Plasma Urate Behaviour, Oedema Score and Presence or Absence of Proteinuria. Numbers of Patients are Given in Parenthe es*

	Prolactin Level	
	Oedema Score >5	*Oedema Score ⩽4*
Rising plasma urate	104·2 ± 15·8* (6)	89·9 ± 8·3* (16)
Steady plasma urate	78·3 ± 6·5* (6)	68·6 ± 3·4* (40)
	Proteinuria Present	*No Proteinuria*
Rising plasma urate	91·6 ± 9·8 (10)	95·5 ± 11·1 (12)

*Difference between means not significant.

Discussion

Prolactin may affect and be affected by changes in sodium and water balance in many vertebrates including some mammals (Lockett, 1965; Horrobin *et al.*, 1971; Ensor *et al.*, 1972; Buckman and Peake, 1973; Jaffe *et al.*, 1973). Prolactin levels are high in pregnancy, and our study shows that they are even higher in pregnancies with pre-eclamptic features. The most significant association was not with the evidence of fluid retention but with a rising plasma urate level; less significant associations occurred with oedema and proteinuria and no association was found with the level of the untreated blood pressure. The association with proteinuria seemed to depend on the common association with a rising urate level. The same could be true for oedema, but there were too few oedematous patients to allow this to be clarified.

Oedema of pregnancy in the absence of renal dysfunction is associated with a good prognosis (Thomson *et al.*, 1967). Proteinuria is a clearer indication of the severity of pre-eclampsia and carries the worst prognosis of the classic triad of pre-eclamptic signs (Butler and Bonham, 1963). A rising plasma urate level is an early sign of pre-eclampsia (Seitchik, 1953), correlates with the characteristic renal biopsy changes (Pollak and Nettles, 1960), and at 32 weeks of gestation is a clear indication of an impaired fetal prognosis (Beilin *et al.*, 1974).

A major problem of this study was to take account of the effect of drugs administered to the patients. Nearly all the drugs used routinely in the treatment of pre-eclampsia increase plasma prolactin levels in non-pregnant patients. Our finding that methyldopa does not increase plasma prolactin levels in pregnancy contrasts with its reported effects in non-pregnant women (Turkington, 1972 b).

In pregnancy, however, baseline plasma prolactin levels are greatly increased and if methyldopa is having any effect on prolactin the effect must be small and obscured by the much larger differences described here. Other drugs used in this study were administered to inpatients only. They included hydrallazine, used in seven patients, sedatives, and an antiemetic (dicyclomine hydrochloride) administered to one patient. The effect of hydrallazine on prolactin secretion has not been studied. The sedatives used were either barbiturates, which experimentally affect prolactin release (Wuttke *et al.*, 1971), or benzodiazepines, which may increase prolactin levels in non-pregnant patients (Fluckiger, 1972). The effects of drugs can be largely excluded by considering the 48 outpatients who took no medication other than methyldopa. In that group the association between high prolactin levels and a rising plasma urate level was still present.

To determine why the plasma prolactin was raised in these circumstances requires separate studies. The weak association with clinical oedema does not suggest that prolactin of itself is a major cause of the fluid retention of pre-eclampsia. That kind of fluid retention characteristically occurs when gross renal impairment has developed with a reduced glomerular filtration rate. The reduced renal function of pre-eclampsia is thought to be due to glomerular endothelial swelling caused by fibrin deposition in the capillary endothelium.

Non-pregnant patients with chronic renal failure have raised prolactin levels for reasons which are not clear (Frantz *et al.*, 1972; Turkington, 1972 a). Only four patients in this study

had a blood urea level above 6·6 mmol/l (40 mg/100 ml) and could be said to have a more than mild degree of renal impairment. The important renal factor in this study was renal tubular dysfunction, as shown by changes in the plasma urate levels. The hyperuricaemia of pre-eclampsia is due to diminished renal tubular excretion and not to excessive production (Chesley and Williams, 1945), and possibly this is due to lactic acidosis caused by anaerobic metabolism in the placenta (Handler, 1960). How prolactin and uric acid metabolism may be linked has yet to be determined, but the possibility that the link is a direct one, in that prolactin may control or modulate uric acid metabolism or excretion during pregnancy, should be considered.

Alternatively, pre-eclampsia may in some way interfere with prolactin clearance. If prolactin is cleared by the kidney, as are some other peptide hormones, then the early involvement of the kidney in pre-eclampsia as measured by plasma urate changes may also indicate a reduced prolactin clearance. Growth hormone (GH), however, which is structurally closely similar to prolactin, is thought to be cleared by the liver, at least in non-pregnant people (Taylor *et al.*, 1972); and the liver is not known to be involved in the early development of pre-eclampsia.

Of the other endocrine changes in pre-eclampsia the reduction in circulating plasma oestrogens (Masson, 1973) provides no explanation of the increased prolactin levels, since plasma oestrogens potentiate prolactin release (Frantz *et al.*, 1972). Human placental lactogen may also be reduced in pre-eclampsia (Letchworth and Chard, 1972) but its relation to prolactin is not known. The levels of adrenocorticotrophic hormone (ACTH) and thyroid-stimulating hormone (TSH), thought to be of pituitary and not placental origin, are raised in pre-eclampsia (Genazzani *et al.*, 1971; Mukherjee and Swyer, 1972). The same may be true of GH, but this is less certain because of the difficulty of its measurement in pregnancy (Laron *et al.*, 1967). That prolactin is also increased gives further evidence that anterior pituitary function may be generally disturbed in pre-eclampsia. TSH and prolactin are both secreted in response to thyrotrophin-releasing hormone (Bowers *et al.*, 1971), and the release of GH and ACTH are also under hypothalamic control. The results suggest that hypothalamic function could be disturbed in pre-eclampsia, and this seems the most likely explanation of these observations.

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Normal Haematological Values: Sex Difference in Neutrophil Count

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Summary

Blood counts were performed on 100 male and 100 female staff to establish normal ranges for our hospital. Neutrophil counts were found to be on average 0·66 × 10^9/l (660/mm^3) higher in women than in men. Statistically this difference was highly significant and was not due to the fact that many of the women were taking oral contraceptives. The neutrophil counts of the men and women were also on average 0·50 × 10^9/l (500/mm^3) greater in the afternoon than in the morning. A correlation was observed between the neutrophil and the monocyte counts.

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Introduction

Patients with absolute neutrophil counts of less than 2·5 × 10^9/l