Early platelet consumption in pre-eclampsia

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Summary and conclusions

One hundred and thirty-one women with chronic hypertension were studied serially during pregnancy to determine the sequence of events in the development of superimposed pre-eclampsia and to discover the time of onset. Twenty-seven women developed a sustained rise in plasma urate concentrations, which began at about 28 weeks' gestation and which is characteristic of pre-eclampsia. The mean platelet count was already significantly reduced and continued to fall until delivery, which was on average at 36 weeks' gestation. A comparable but smaller decrease in platelet count was seen in 55 women who had borderline but consistent increases in plasma urate concentrations. In 49 women whose plasma urate concentrations remained steady the platelet count did not change significantly before delivery.

The reduced platelet count in women who develop pre-eclampsia suggests that increased platelet consumption is an early feature of the disorder.

Introduction

Changes in the coagulation system in established pre-eclampsia are well documented^{1,2} and distinguish pre-eclampsia from chronic hypertension coinciding with pregnancy.³ The time of onset of the coagulation disturbance is a matter of controversy, but longitudinal studies have suggested that it is a late secondary feature of pre-eclampsia.^{4,5} The most definitive examination of the problem⁶ was inconclusive because no severe cases of pre-eclampsia developed in the 60 primigravidae selected for serial investigation.

In a preliminary study of the evolution of severe pre-eclampsia we found that a fall in the circulating platelet count occurred earlier in pre-eclampsia than had been suspected.⁷ We therefore expanded this investigation and studied chronically hypertensive women, who have a high risk of developing pre-eclampsia⁸ and whose coagulation indices³ do not differ from those of normal women. As an index of the development of superimposed pre-eclampsia⁹ we used serial plasma urate concentrations. This is a new technique, which was used for the first time in this study. The onset of superimposed pre-eclampsia occurs at the point when the plasma urate concentration begins to rise.

Patients and methods

Hypertension was diagnosed in pregnant women if on two occasions at least 24 hours apart the systolic or diastolic pressure equalled or

exceeded 140 or 90 mm Hg respectively. To minimise observer bias a London School of Hygiene sphygmomanometer was used. Patients with known hypertension who became pregnant while taking anti-hypertensive drugs were admitted to the study without blood-pressure screening. They were then assessed as inpatients to give baseline data, and were followed up at an antenatal hypertension clinic. Blood was sampled at least monthly until 28 weeks and then at least fortnightly until delivery. Patients were not recruited into the study after 28 weeks, and only those whose pregnancy continued for 42 days or more after the first assessment are included in the analysis; this was to ensure that patients did not have early pre-eclampsia when first assessed. Antihypertensive drugs were used in some patients but not diuretics.

Venous blood was anticoagulated with EDTA, aspirated into plastic sedimentation tubes, and allowed to settle for about 30 minutes. Platelets were counted in the platelet-rich plasma by means of a Thrombocounter (Coulter Electronics Limited). The whole-blood platelet count was calculated from the packed cell volume of the same sample.¹⁰

Plasma urate concentrations were measured in heparinised blood by the automated colorimetric hydroxylamine method (SMA 12/60). The clinical and laboratory readings were transferred to a computer record for analysis. Blood-pressure changes could not be used as a measure of the development of pre-eclampsia because some patients were receiving hypotensive drugs. The onset of renal manifestations of pre-eclampsia was defined by a rise in plasma urate concentration above the baseline value.

A definite increase in plasma urate concentration was recorded when it rose at least 120 $\mu\text{mol/l}$ (2 mg/100 ml) above the baseline measurement on two successive occasions, usually one or two weeks apart. The time that the increase began was defined as the time of the first follow-up visit at which the plasma urate concentration was consistently 60 $\mu\text{mol/l}$ (1 mg/100 ml) above the baseline reading. A borderline increase in plasma urate concentration was defined as 30 $\mu\text{mol/l}$ (0.5 mg/100 ml) above the baseline measured on three successive occasions, the time at which it began being taken as the time of the first measurement. Patients with no consistent change in plasma urate concentration served as controls. Changes in platelet counts were determined in relation to the point at which the plasma urate concentration first began to increase. The control patients were matched for gestational maturity with the patients whose plasma urate concentrations showed changes characteristic of pre-eclampsia. Results from both groups were analysed and compared. All analyses were carried out "blind" by computer, so that the time of onset of a rise in plasma urate concentration was calculated without knowledge of the platelet counts.

Proteinuria was diagnosed when two midstream specimens of urine contained 0.2 g or more of protein/l without evidence of infection or when one midstream specimen contained 1.0 g or more/l without evidence of infection.

Results

Of the 131 women studied, 27 developed an increase in plasma urate concentration diagnostic of the renal changes of severe pre-eclampsia at a mean time of 206 days (table I). Fifty-five women had borderline increases characteristic of mild pre-eclampsia, which were first detectable at a mean time of 247 days. The remaining 49 "normal" women had no consistent change in plasma urate concentrations.

The characteristics of the three groups were similar (table II). The normal women included slightly more multiparae than did the other two groups, but the difference was not significant. The one perinatal death in this group was caused by rhesus isoimmunisation. In the group with definitely increased plasma urate concentrations the mean maternal height was significantly less than in the other groups. The one perinatal death was caused by severe pre-eclampsia. Compared with the control group there was both a significant excess of small babies and a deficit of large babies, and maturity at delivery was significantly reduced, reflecting the severity of the pre-eclampsia ($P < 0.01$; Student's t test).

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TABLE I—Mean maturity at time of booking, onset of pre-eclampsia, and delivery in the three groups with definitive, borderline, or no increase in plasma urate concentrations

Group	Mean maturity in days (± 1 SD)			
	At booking	At time of rising plasma urate concentrations		At delivery
		Severe PET	Mild PET	
Definite (n = 27)	134 $\pm$ 31	206 $\pm$ 31	—	253 $\pm$ 20
Borderline (n = 55)	151 $\pm$ 33	—	247 $\pm$ 17	267 $\pm$ 5
No increase (n = 49)	154 $\pm$ 34	(210 $\pm$ 20*)	(244 $\pm$ 12*)	266 $\pm$ 9

PET = Pre-eclamptic toxæmia.

*Times at which these patients were observed chosen to match those in the two groups with pre-eclampsia.

TABLE II—Characteristics of patients in the three groups with definite, borderline, or no increase in plasma urate concentrations

	Group		
	Definite	Borderline	No increase
No in group	27	55	49
Mean age in years (± 1 SD)	27.6 $\pm$ 3.8	27.7 $\pm$ 5.2	27.1 $\pm$ 6.4
Mean height in cm (± 1 SD)	160.4 $\pm$ 5.8*	163.3 $\pm$ 5.7	163.1 $\pm$ 4.6
No (%) of primigravidae	15 (55.6)	30 (54.5)	20 (40.8)
No (%) with proteinuria	10 (37.0)	0	0
Mean maximum blood pressure (mm Hg)	170/107†	151/97	155/99
No (%) on antihypertensive drugs at delivery	15 (56)	24 (44)	10 (20)
No of perinatal deaths	1	0	1
Mean birthweight in g (± 1 SD)	2500 $\pm$ 800	3100 $\pm$ 400	3200 $\pm$ 500
No (%) of births weighing ≤ 2000 g	9 (33.3)‡	0 (0)	1 (2.0)
No (%) of births weighing ≥ 3500 g	1 (3.7)‡	11 (20.0)	13 (26.5)

*Compared with group with no pre-eclampsia: $t = 2.08$; $P < 0.02$.

†For both systolic and diastolic pressures compared with group with no pre-eclampsia: Mann-Whitney U test; $P < 0.01$.

‡For both excess of small babies and deficit of large babies compared with group with no pre-eclampsia: Fisher's exact test; $P < 0.001$.

More patients in the groups with increased plasma urate concentrations were receiving antihypertensive treatment, so that strict comparisons between mean blood pressures could not be made. Nevertheless, the mean maximum blood pressure in the group with definitely increased plasma urate concentrations was significantly above the means of the two other groups. Furthermore, proteinuria was seen in 10 (37%) of the patients in this group but in none of the other patients.

Initially the three groups had similar mean platelet counts. In the 49 women whose plasma urate concentrations remained constant throughout there was no significant change in mean platelet count (figs 1 and 2). Compared with this group, both groups with hyperuricaemia had significantly lower platelet counts by the time of delivery.

FIG 1—Serial platelet counts and plasma urate concentrations in normal patients and those with pre-eclampsia (mean ± 1 SE of mean). * $P < 0.05$. *** $P < 0.01$.

Conversion: SI to traditional units—Plasma urate: $1 \mu\text{mol/l} \approx 16.8 \mu\text{g/100 ml}$.

In the more severely affected group this difference had already been established by the time the consistent rise in plasma urate concentration began—that is, at 29 weeks, or about seven weeks before delivery (fig 1). At the two earlier examinations the mean platelet counts had already begun to fall, but the difference from that of the normal group was not significant. The group with borderline increases in plasma urate concentrations had similar but less pronounced changes in the mean platelet count, with a small but consistent reduction already developed by 32 weeks, about six weeks before delivery (fig 2).

FIG 2—Serial platelet counts and plasma urate concentrations in normal patients and those with borderline pre-eclampsia (mean ± 1 SE of mean). * $P < 0.05$. *** $P < 0.01$.

Conversion: SI to traditional units—Plasma urate: $1 \mu\text{mol/l} \approx 16.8 \mu\text{g/100 ml}$.

Discussion

The question whether the platelet count falls as normal pregnancy progresses is controversial.¹¹ Fenton *et al* reported no change in a serial study of one cohort of women,¹² which agrees with our observations in patients who did not develop the renal changes of pre-eclampsia. Our study of platelet counts in pregnancy was the first to use plasma urate measurements to determine the onset and progression of pre-eclampsia. This permitted objective identification and exclusion of patients with borderline as well as established features of pre-eclampsia. The results suggest that a falling platelet count in pregnancy is primarily a feature of pre-eclampsia. Other studies reporting a falling platelet count in the third trimester of normal pregnancy may have been biased by the inclusion of undiagnosed cases of pre-eclampsia. Our observations also show that this reduction in platelet count occurs early in the development of pre-eclampsia, being detectable about seven weeks before delivery. This confirms our earlier, smaller study.⁷

The lower platelet counts in severe pre-eclampsia are associated with abnormal activation of the coagulation system and are believed to reflect increased platelet consumption. Probably, platelet consumption is increased before lower counts are detected, which raises the question of what part platelet-count and coagulation changes play in the aetiology of pre-eclampsia. In particular, it is not clear whether these peripheral changes are a cause or a consequence of the occlusive vascular lesions in the uteroplacental arteries associated with fetal growth retardation.¹³

Because of the variation in counts between patients no diagnostic importance can be attached to a single low reading; thus platelet counts would not be a good screening test for pre-eclampsia. They are simpler to obtain than other measurements of disturbed coagulation, however, and repeated readings in the same patient can be useful in showing a consistent trend towards lower counts, which may herald the onset of pre-eclampsia. Thus the platelet count can be helpful in monitoring high-risk pregnancies.

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Duodenal ulcer and working-class mobility in an African population in South Africa

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Summary and conclusions

The number of Africans in Johannesburg presenting with duodenal ulcers has steadily increased over the past 50 years. The characteristics of 105 patients with duodenal ulcer who presented at Baragwanath Hospital were compared with those of matched and unmatched samples of patients without gastrointestinal conditions in the same hospital. Men with duodenal ulcers were found to be significantly better educated than their controls, most had been born in the town, and more of them were employed at higher, though not the highest, educational levels.

These data were used to test Susser's proposition that duodenal ulcers are associated with "early urbanisation." Johannesburg blacks with duodenal ulcer did seem to fit the pattern, but the relation between stress and duodenal ulcer remains unclear.

Introduction

Duodenal ulcer is rarely reported in the rural black population of South Africa.¹ Until recently this was also true among urban blacks: Beyers² reported only three cases among 18 000 hospital

admissions in Johannesburg in 1921-6 (0.02%). There has, however, been a steady increase in the number of cases over the past 50 years. Thus Eagle and Gillman³ found 13 cases of duodenal ulcer in 9472 necropsies performed in 1928-37 (0.14%); Bremner⁴ reported 87 cases among 31 500 (0.28%) admissions to the surgical section of the Johannesburg General Hospital in 1964-71; and in 1976 105 patients with newly diagnosed duodenal ulcer were admitted to Baragwanath Hospital medical and surgical wards out of a total of 23 244 adult admissions (0.45%). We examined some of the characteristics of these urban black patients and compared them with selected control groups. We propose here some hypotheses that may explain any differences noted. Our study was thus exploratory rather than definitive.

Patients and methods

The series consisted of the 105 patients who presented, either as inpatients or outpatients, at Baragwanath Hospital, Johannesburg, during 12 months in 1976-7 and who were found to have duodenal ulcers. Diagnosis was based on clinical and radiological examination and, in most cases, endoscopy. Thirty-five of the patients, who were available either as inpatients or outpatients over four weeks in 1976, were subjected to more intensive interviewing by a physician and, separately, by a trained sister under the direction of a social anthropologist. The detailed findings relating to this subgroup will be presented in another paper, though some of the data are presented here.

One hundred and five patients without traumatic or gastrointestinal conditions were matched with the patients for age, sex, and inpatient or outpatient status. They were selected and substituted (as control quotas were filled) at random, and were interviewed over three weeks in August and September 1977. A second unmatched control group was interviewed over one week in September 1977. We wanted equal numbers of men and women and excluded those with trauma or gastrointestinal conditions, but otherwise the unmatched controls were selected at random. The final sample comprised 33 men and 35 women.

Several questionnaires were used. These included the medical officer's schedule (short), the medical officer's schedule (long), the sociological schedule, and an anxiety schedule (to which were added, when administered alone, several biographical questions). All but the sociological schedule were highly structured. The sociological schedule, however, comprised a number of open-ended questions, and interviews were conducted as informally as possible. Anxiety was measured by the Taylor Manifest Anxiety scale⁵ adapted by Mr

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