

Platelet count and liver function tests in proteinuric and chronic hypertension in pregnancy

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Summary

Platelet counts and plasma enzyme estimations were performed in 207 pregnant patients with proteinuric hypertension and in 60 patients with chronic hypertension. Patients with abruptio placentae were excluded. In the proteinuric hypertensive patients a low platelet count ($< 150\,000/\text{mm}^3$) was found in 63 (30%) and elevated transaminase levels in 50 (24%) and both abnormalities were present in 47 patients (23%). The serum lactate dehydrogenase (LDH) value was mildly elevated in most proteinuric hypertensive women, but a markedly elevated LDH level ($> 400\text{ IU/l}$) was usually associated with other evidence of liver necrosis. Raised plasma alkaline phosphatase and γ -glutamyltransferase levels were not related to the occurrence or severity of liver necrosis. In proteinuric hypertensive patients a low platelet count or elevated transaminase level was associated with deteriorating renal function, increased maternal morbidity, increased incidence of low-birth-weight babies and a raised perinatal mortality rate (149/1 000). In patients with chronic hypertension, 1 had a low platelet count but none had elevated transaminase, LDH or other enzyme levels and there was no recorded perinatal mortality.

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Pre-eclampsia may affect both the haemostatic system and liver function. Platelet activation and turnover are increased, resulting in a reduced platelet count and this is associated with disseminated intravascular coagulation (DIC) in many, but not all, patients with proteinuric hypertension in pregnancy.¹⁻³ Liver function, as measured by assays of plasma enzymes, may also be impaired in patients with proteinuric hypertension.⁴ Two basic lesions have been described in post-mortem liver biopsies of eclamptic women: periportal haemorrhages and ischaemic necrosis.⁵ A low platelet count and abnormal liver function tests often occur simultaneously^{4,6} and, if both are present, micro-angiopathic haemolytic anaemia is invariably present. Weinstein⁷ used the acronym HELLP (Haemolysis, Elevated Liver enzymes, and Low Platelets) for this entity, and suggested that it should be regarded as a complication of severe pre-eclampsia. The incidence in pre-eclampsia has been reported to be about 10%, and the occurrence of the HELLP syndrome is associated with considerable maternal and perinatal morbidity and mortality.^{8,9}

At Groote Schuur Hospital Maternity Centre, Cape Town, we gained the impression that low platelet counts and raised plasma enzyme levels were more common than had previously been described. Earlier studies of pre-eclamptic patients included many cases of abruptio placentae, which may have been responsible for the DIC and liver dysfunction, and increased perinatal mortality.

A study was designed to try to answer the following questions: (i) what is the incidence of a low platelet count and/or abnormal plasma transaminase values in proteinuric hypertensive patients presenting at this hospital? (ii) is a low platelet count always accompanied by abnormal plasma transaminase levels? (iii) which of the routinely performed plasma enzyme assays provide the best indication of hepatic involvement? and (iv) if patients with abruptio placentae are excluded, is the

finding of a low platelet count and/or abnormal transaminase levels associated with increased maternal and perinatal mortality?

Patients and methods

Groote Schuur Hospital Maternity Centre is the referral unit for the Peninsula Maternal and Neonatal Services (PMNS) and had a total of 26 123 deliveries in 1988. This study was started on 1 April 1989 and ended on 10 November 1989. The hypertensive disorders of pregnancy were classified according to Davey and MacGillivray,¹⁰ and patients with proteinuric hypertension and chronic hypertension were recruited for the study. 'Proteinuric hypertension' includes 'gestational' and 'unclassified' proteinuric hypertension and 'pre-eclampsia' superimposed on known chronic hypertension. In the 'unclassified' proteinuric hypertension group, all the patients became non-proteinuric after delivery and, in retrospect, could be classified as 'gestational'. Patients with the following conditions were excluded: (i) abruptio placentae; (ii) chronic renal disease, including patients booking in early pregnancy with both hypertension and proteinuria; (iii) known diabetes mellitus; (iv) other medical disorders that might interfere with blood coagulation or liver function (e.g. severe anaemia, leukaemia, liver disorder); and (v) absence of blood samples taken in the 48 hours before or the 24 hours after delivery.

Platelet counts were measured by a Coulter Full Blood Count Analyser. If the platelet count was found to be low ($< 150\,000/\text{mm}^3$),¹¹ a Thrombo-C test was performed on a Seguoia-Turner Whole Blood Platelet Analyser (Mountain View, Calif, USA). The plasma liver enzyme and plasma creatinine values in serum were measured by a SMAC II Auto Analyser. If the serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were above the normal range on the SMAC Auto Analyser (> 40 IU/l and 53 IU/l, respectively), the plasma enzyme levels were measured with kinetic assay kits (Boehringer Diagnostics Inc., Somerville, NJ, USA). The published normal ranges are AST — $7 - 25$ IU/l, and ALT — $1 - 25$ IU/l, respectively; transaminase levels are not altered by pregnancy.¹² All samples with a raised γ -glutamyltransferase (GGT) concentration on Auto-Analyser (> 50 IU/l; normal < 40 IU/l) were also confirmed by a kinetic assay (Boehringer Mannheim GmbH, Germany). Only when both AST and ALT were raised was the liver function considered to be abnormal. Plasma creatinine values were considered to be abnormal if $> 82 \mu\text{mol/l}$ (> 2 SD above the mean for pregnancy).¹³

The results of the liver function tests shown in the Tables and Figures are the highest levels recorded in each patient. The results of the laboratory tests in proteinuric hypertensive patients with normal platelet counts and normal transaminase levels, and in chronic hypertensive patients, were those performed on samples taken closest to delivery (either in the 48-hour period before or the 24-hour period after delivery).

The statistical significance of the differences in the numbers of patients with abnormal tests in each group was analysed by the χ^2 test or by the Fisher's exact test if the expected cell frequency was < 5 .

Results

We studied 207 consecutive patients who presented with proteinuric hypertension and 60 consecutive patients who presented with chronic hypertension in pregnancy.

Maternal characteristics and fetal outcome

Patients with proteinuric hypertension were younger and of lower parity than chronic hypertensive patients (Table I), 44%

of the women with proteinuric hypertension being primigravid. The mode of delivery, fetal birth weight, and maternal and perinatal mortality in the two groups are shown in Table II.

TABLE I. AGE, RACE AND PARITY OF PATIENTS

	Proteinuric hypertension		Chronic hypertension	
	No.	%	No.	%
Age (yrs)				
< 20	42	20	1	2
20 - 34	148	72	38	63
≥ 35	17	8	21	35
Race				
Black	85	41	15	25
Cape Coloured	120	58	45	75
White	2	1	—	—
Parity				
0	91	44	7	12
1 - 3	97	47	39	65
≥ 4	19	9	14	23

TABLE II. MODE OF DELIVERY, BIRTH WEIGHT AND MATERNAL/PERINATAL MORTALITY

	Proteinuric hypertension		Chronic hypertension	
	No.	%	No.	%
Delivery				
Total	207		60	
Spontaneous	56	27	33	55
Instrumental	18	9	4	7
CS	133	64	23	38
Birth weight (g)				
< 1 000	28	13	0	
1 000 - 1 999	81	38	4	7
2 000 - 2 999	78	37	27	44
$\geq 3\,000$	24	11*	30	49†
Maternal mortality	2	1	0	
Perinatal mortality	22	11	0	
Eclampsia	16	8	0	

* 4 twin pregnancies.

† 1 twin pregnancy.

The seemingly high caesarean section (CS) rate of 64% in the proteinuric hypertension group is because a large number of the patients required delivery before 34 weeks' gestation for either fetal distress and/or growth retardation or maternal complications. Fifty-one per cent of the infants of the women with proteinuric hypertension and only 7% of the infants of chronic hypertensive mothers had birth weights of less than 2 000 g. The perinatal mortality rate was 106/1 000 in the proteinuric hypertension group compared with 29.5/1 000 for the whole PMNS region. In the chronic hypertension group, there was no recorded perinatal or maternal mortality. There were 2 maternal deaths in the women with proteinuric hypertension and the eclampsia rate was 8%.

Platelet count and plasma transaminases

Of the proteinuric hypertension patients 30% had a low platelet count ($< 150\,000/\text{mm}^3$) and 24% had elevated plasma

transaminase levels during pregnancy. Of patients with a low platelet count, 75% also had elevated transaminase levels and 94% of patients with abnormal transaminase levels had a low platelet count. Both a low platelet count and an abnormally raised transaminase level were found in 23% of patients. There was a wide variation in the degree of thrombocytopenia and the levels of plasma transaminase. Of the patients with thrombocytopenia, 24% had a platelet count of $< 50\,000/\text{mm}^3$ and transaminase levels were often highly elevated (more than 10-fold).

Total bilirubin levels (normal range 1 - 17 $\mu\text{mol/l}$) were elevated in 52% of the women with abnormal transaminase levels, but the increase was small in the majority of patients (15 patients $< 34\ \mu\text{mol/l}$; 8 34-85 $\mu\text{mol/l}$). In 3 patients, however, the bilirubin levels were increased more than 5-fold ($> 85\ \mu\text{mol/l}$) and all 3 had renal failure. The liver dysfunction and the renal failure returned to normal after delivery in 2 of these 3 women but the third patient died of combined hepatic and renal failure.

Only 1 patient with chronic hypertension had a marginally low platelet count and none of the patients with chronic hypertension had abnormal serum transaminase or bilirubin levels.

Plasma lactate dehydrogenase (LDH)

Most of the proteinuric hypertensive patients with abnormal transaminase levels also had markedly elevated LDH levels ($> 400\ \text{IU/l}$) (Fig. 1). Of the patients with proteinuric hypertension but with normal platelet counts and transaminase levels, 63% had raised LDH levels but the increase was small — less than twice the normal range (200 - 399 IU/l). Of patients with chronic hypertension and normal platelet counts and transaminase levels 24% had mildly raised plasma LDH.

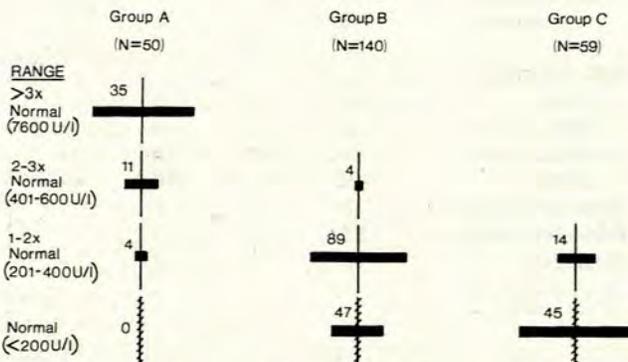


Fig. 1. LDH levels in patients with proteinuric and chronic hypertension. The length of the solid bars represents the relative percentage of patients in each group with an LDH value in that particular range (group A — proteinuric hypotension + abnormal transaminases; group B — proteinuric hypertension + normal platelets and transaminases; group C = chronic hypertension).

Plasma alkaline phosphatase (AP)

AP levels were increased above the normal non-pregnant range (30 - 115 IU/l) in most patients owing to the normal placental production of this enzyme, the increase occasionally reaching concentrations more than 3 times the normal non-pregnant mean. There was, however, no difference between the AP levels of patients with proteinuric or chronic hypertension (Fig. 2). Plasma AP concentrations did not correlate with the level of transaminase in proteinuric hypertension and patients with significantly raised bilirubin levels often had normal AP concentrations.

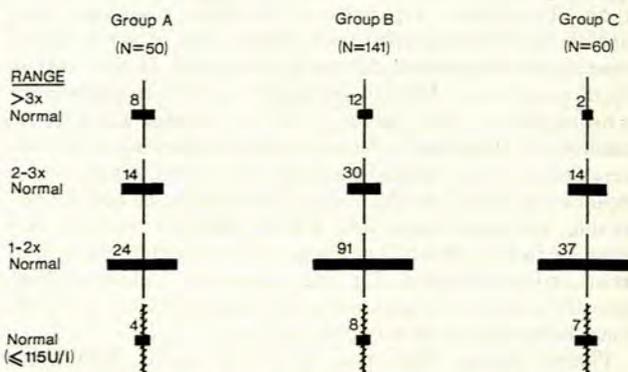


Fig. 2. Alkaline phosphatase levels in patients with proteinuric and chronic hypertension. The length of the solid bars represents the relative percentage of patients in each group with an alkaline phosphatase value in that particular range (group A — proteinuric hypotension + abnormal transaminases; group B — proteinuric hypertension + normal platelets and transaminases; group C = chronic hypertension).

Plasma GGT

GGT levels were raised in only 36% of proteinuric hypertension patients with abnormal transaminase levels. Of 26 patients with both raised transaminase and bilirubin levels only 8 had a raised GGT. Abnormally raised GGT levels were found in a few isolated patients; this appeared unrelated to the severity of the disease or other findings (Table III). The raised GGT levels in these patients were probably due to alcohol abuse and were associated with other indices of excessive alcohol intake, e.g. a high mean corpuscular volume of erythrocytes.

Maternal and perinatal morbidity and mortality

The maternal mortality, eclampsia rate, perinatal mortality and incidence of infants with a birth weight of $< 2\,000\ \text{g}$ and serum creatinine levels in the proteinuric hypertensive patients

TABLE III. GGT LEVELS

	Proteinuric hypertension and abnormal transaminase levels (N = 50)		Proteinuric hypertension and normal transaminase levels (N = 141)		Chronic hypertension (N = 60)	
	No.	%	No.	%	No.	%
Normal ($< 50\ \text{IU/l}$)	32	64	128	95	57	97
Abnormal ($\geq 50\ \text{IU/l}$)	18	36	7	5	2	3

TABLE IV. MATERNAL AND PERINATAL MORBIDITY AND MORTALITY

	Proteinuric hypertension and abnormal platelet count and/or transaminase levels (N = 50)		Proteinuric hypertension and normal platelet count and/or transaminase levels (N = 141)		Chronic hypertension (N = 60)	
	No.	%	No.	%	No.	%
Maternal mortality	2/66		—		—	
	(30/1 000)					
Eclampsia	6/66	9	10/141	7	—	
Serum creatinine ($\mu\text{mol/l}$)						
> 82	40/65	62*	36/140	26	2/58	3
> 250	6/65	9*	—		—	
Perinatal mortality	10/67		12/144		—	
	(149/1 000)**		(83/1 000)			
Birth weight						
< 2 000 g	44/67	66***	65/144	45	4/61	7

* $P < 0,001$ compared with groups with proteinuric hypertension and normal platelets, and chronic hypertension.

** $P < 0,002$ compared with group with chronic hypertension.

*** $P < 0,05$ compared with group with proteinuric hypertension and normal platelets, and $P < 0,001$ compared with group with chronic hypertension.

with abnormal platelet counts and/or transaminase levels were compared with those in proteinuric hypertensive patients with normal platelet counts and normal transaminase levels (Table IV). In the proteinuric hypertensive patients with abnormal platelet counts and/or transaminase levels the perinatal mortality rate was significantly increased at 149/1000 compared with 83/1000 in the group with normal platelet counts and transaminase levels. The incidence of low-birth-weight infants of 66% was also higher in the former group compared with 45% in the latter group.

Of the proteinuric hypertensive patients with abnormal platelet counts or transaminase levels 62% had a serum creatinine value of more than 82 $\mu\text{mol/l}$ and 6 patients had a value of more than 250 $\mu\text{mol/l}$. The 2 maternal deaths in this series occurred in this latter group. There was no significant difference in the eclampsia rate in the proteinuric hypertensive women with and without abnormal platelet counts or transaminase levels.

Discussion

The incidence of low platelet counts (30%) and of elevated plasma transaminase levels (24%) in women presenting with proteinuric hypertension at Groote Schuur Hospital Maternity Centre was much higher than the reported incidence of 10 - 12% of the so-called HELLP syndrome in other centres.^{9,14} The high incidence of low platelet counts in proteinuric hypertensive women at Groote Schuur Hospital is, however, comparable with the 29% in the series on eclamptic women delivered at Parkland Memorial Hospital, Dallas, Texas, USA.² A low platelet count and elevated plasma transaminase level were very commonly associated. Patients with abnormal transaminase levels almost always (94%) had a low platelet count, but in 25% of patients with a low platelet count the transaminase levels were within the normal range. A low platelet count without a raised transaminase value may represent an earlier stage of a multisystem disorder.

The plasma enzyme measurements performed are relatively nonspecific assays of intracellular enzymes that are normally present in many tissues and are released into the circulation after cell necrosis or lysis, causing an increase in plasma concentration. Elevated concentrations of plasma AST and

ALT levels are indicative of liver cell necrosis and sensitive kinetic assays were therefore used to provide a more accurate measure of these enzymes in all patients with raised plasma transaminase levels on routine screening. Elevated transaminase levels due to damage to the heart, kidney or muscles can, in general, be excluded in this study, and raised levels of these enzymes may therefore be regarded as providing a measure of liver necrosis and liver cell damage. Of the two transaminases, a high serum ALT concentration is more specific for liver cell necrosis than a raised serum AST level, since the concentration of ALT is relatively higher in the liver than in other tissues. In women with normal serum ALT concentrations, isolated marginally increased AST concentrations (between 1 and 1,5 times the normal range) were sometimes observed, probably due to haemolysis of the blood specimen because AST concentrations are higher in red blood cells.¹⁵

Of the other plasma enzymes routinely measured, LDH may also be an indicator of liver involvement in proteinuric hypertensive patients with normal transaminase levels. Mildly raised LDH levels (less than twice the normal range) were frequently found. This could have been due to haemolysis of blood specimens, since LDH concentrations are also high in erythrocytes.¹⁵ When plasma transaminase levels were raised, however, LDH levels were, on average, always very high — with LDH concentrations of more than 400 U/l. Most of the increase in LDH concentrations is reported to be due to an increase in LDH iso-enzymes 1 and 2, which are mainly of erythrocyte origin.⁶ Further studies of the LDH iso-enzyme levels are necessary in both normal and proteinuric hypertensive women in pregnancy to determine how much of the raised LDH level is due to haemolysis of the blood specimens and how much is due to liver necrosis.

Maternal morbidity is also increased in proteinuric hypertensive patients with abnormal platelet counts or transaminase levels and renal failure occurred in a number of these women, even in the absence of abruptio placentae. The perinatal mortality rate in the proteinuric hypertensive group with abnormal platelet counts and transaminase levels was 5 times higher than the average PMNS perinatal mortality and approximately double that of proteinuric hypertensive women with normal platelet counts and transaminase levels. The incidence of low birth weight in infants was also higher in the proteinuric hypertensive patients with abnormal compared with normal platelet counts and transaminase levels. The high

incidence of low-birth-weight infants was due to many of the patients having to be delivered prematurely due to fetal compromise.

The cause of the increased platelet consumption and the liver necrosis in proteinuric hypertensive mothers is not known, but there is evidence that the coagulation cascade is activated by injury to the endothelial cells of small vessels in pre-eclampsia.¹⁶ There is also considerable evidence of prostacyclin deficiency in the uteroplacental unit and, to a lesser extent, in the general circulation in pre-eclampsia.¹⁷ A low platelet count is indicative of a moderate to severe DIC, which could well be associated with fibrin deposition and thrombosis in liver sinusoids causing liver necrosis. Similar fibrin deposition could occur in the renal arterioles causing decreased glomerular function and possibly the occurrence of proteinuria. It is possible that the deficiency in prostacyclin and the decrease in the prostacyclin/thromboxane ratio may be more marked in certain organs, such as the utero-placental unit, kidney and liver, possibly due to a factor inhibiting prostacyclin synthetase. This would result in intravascular coagulation and fibrin deposition within these organs, and consequent ischaemia and cell damage and necrosis. Disseminated and local intravascular coagulation is a serious complication of proteinuric hypertension in pregnancy resulting in both maternal and perinatal morbidity and mortality.

The high incidence of low platelet counts and raised plasma transaminase levels in women with proteinuric hypertension and the serious prognostic implications make repeated measurements of the platelet count and plasma enzyme levels an essential part of the management of all such patients. These tests are often the only indication that a multisystem disorder has developed and that the clinical condition of the mother is serious and requires urgent treatment and delivery of the fetus. Low-dose aspirin has recently been claimed to prevent pre-eclampsia by virtue of its action in preferentially inhibiting thromboxane synthetase in platelets compared with prostacyclin synthetase in the vascular endothelium so increasing the prostacyclin/thromboxane ratio.¹⁸ It would therefore be of considerable interest to see whether low-dose aspirin can prevent or reduce the high incidence of thrombocytopenia and liver necrosis in pre-eclampsia and whether it can reverse this disorder once it has started.

In conclusion, proteinuric hypertension is frequently associated with a low platelet count and raised plasma transaminase levels, whereas, in contrast, chronic hypertension is rarely if

ever associated with these abnormalities. The development of thrombocytopenia or impaired liver function is of major significance in all patients with hypertension in pregnancy and is an indication for routine platelet counts and liver enzyme estimations — certainly in all patients with proteinuric hypertension, since early recognition is essential to prevent maternal and perinatal mortality and morbidity.

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