Are high uric acid levels in patients with early pre-eclampsia an indication for delivery?

H J Odendaal, M E Pienaar

Objective. To compare the perinatal mortality rates of pre-eclamptic patients with high, normal and low uric acid levels.

Design. Prospective analytic study.

Setting. Tertiary hospital to which many patients with severe pre-eclampsia are referred.

Subjects. Two hundred and twenty-nine patients with severe pre-eclampsia.

Intervention. Delivery for maternal or fetal reasons, not taking uric acid levels into account.

Main outcome measure. Perinatal mortality rate.

Results. The mean uric acid level prior to delivery at a mean gestational age of 30.9 weeks was 0.4 mmol (SD 0.11). Twenty patients had uric acid levels of 0.28 mmol/l or lower and 25 patients values of 0.52 mmol/l or higher. The mean gestational age at admission and the admission-delivery interval for the high, normal and low uric acid groups were 29.2 weeks, 11.8 days; 29.2 weeks, 13.3 days and 27.1 weeks, 13 days respectively. For babies who weighed 1 000 g or more at delivery, the perinatal mortality rates were 40, 11 and 50 respectively.

Conclusion. There is no evidence from this study to support the association between perinatal deaths and higher uric acid levels in patients with severe pre-eclampsia.

S Afr Med J 1997; **87:** 213-218.

Plasma urate levels in pregnancy increase before patients develop pre-eclampsia.[1,2] Perinatal mortality is markedly raised when maternal plasma urate concentrations are raised, especially when the pre-eclampsia is of early onset.[3,4] Plasma urate concentrations above the normal level in patients with pre-eclampsia are also associated with low birth weight[5] and growth retardation.[6] Rapidly rising urate levels have been demonstrated to predict fetal distress reliably.[6] For these reasons it has been suggested that the pregnancy be terminated when urate levels increase rapidly in patients with pre-eclampsia.[5] But the predictive value of

Department of Obstetrics and Gynaecology, University of Stellenbosch and Tygerberg Hospital, Tygerberg, W Cape

H J Odendaal, MB ChB, FCOG (SA), FRCOG, MD

MRC Perinatal Mortality Research Unit, Tygerberg, W Cape

M E Pienaar, MB ChB, MMed

high uric acid levels has also been questioned, given that values of normal and pre-eclamptic patients frequently overlap.[7]

However, the reports on increased perinatal mortality were published some time ago,[3,4] before the value of frequent fetal heart rate monitoring in patients with severe pre-eclampsia became known.[8] In the meantime it has also been demonstrated that expectant management of patients with severe pre-eclampsia improves perinatal outcome and that neonatal survival largely depends on gestational age at delivery.[9,10] In these studies we frequently observed high maternal uric acid values in patients whose fetal heart rate patterns remained normal for several days or even weeks. We therefore began to question the necessity to deliver patients with severe pre-eclampsia because they had high uric acid values. We therefore analysed uric acid values in 229 patients with severe pre-eclampsia.

Methods

The definition and management of severe pre-eclampsia have been described previously.[9,11] In these studies, treatment entailed the administration of magnesium sulphate for 24 hours after admission and the tight control of blood pressure. Dihydralazine was used for acute control. Thereafter methyldopa was used, with prazosin as the second and nifedipine as the third drug, to maintain the blood pressure between 140/90 and 150/100 mmHg. The fetal heart rate was monitored at least every 6 hours for the early detection of fetal distress caused by a possible sudden onset of abruptio placentae. Patients were delivered once a gestational age of 34 weeks had been reached or when maternal reasons or abnormal fetal heart rate patterns were an indication for earlier delivery. Tygerberg Hospital growth curves were used to assess whether newborns were small for gestational age.[12]

Blood was taken for uric acid estimation on admission and twice a week until delivery. For this study only the level from the last test was analysed. Plasma uric acid was assayed by the automated urikinase method on a Technican SMAC machine. At 0.15 mmol/l our laboratory's coefficient of variation is 10.9%, at 0.55 mmol/l 2.8% and at 0.91 mmol/l 1.7%. The method of analysis did not change during the study period.

Firstly, the means and standard deviations (SDs) of the uric acid levels were assessed. Patients were then divided into three groups: a high uric acid group with levels 1 SD above the mean, a normal group and a low uric acid level group where the values were 1 SD below the mean. These three groups were then compared in respect of perinatal outcome. Means were compared with Student's *t*-test or the Mann-Whitney U-test when the distribution of results was not normal. Proportions were compared with a chi-square test or, when the numbers were small, Fisher's exact test. A *P*-value of less than 0.05 was regarded as significant.

Results

The mean uric acid level of the 229 patients was 0.4 mmol/l and the standard deviation 0.11. Twenty-five patients had uric acid levels $\geq$ 0.52 mmol/l, 184 patients had values of 0.4 $\pm$ 0.11 mmol/l and 20 patients had values $\leq$ 0.28 mmol/l. The mean ages of patients in these three groups were 27 years, 26 years and 26.8 years respectively (Table I). The proportions of primigravidas ranged from 24% in the high uric acid group to 35% in the normal group. Four patients (17%) in the high uric acid group gave a history of hypertension prior to pregnancy as did 4 patients (25%) in the low uric acid group. Six patients (24%) in the high uric acid group received no antihypertensive drugs, 17 (68%) one or two drugs and 2 (8%) more than two drugs. In the normal uric acid group these numbers were 66 (36%), 101 (55%) and 17 (9%) respectively. In the low uric acid group 10 (50%) patients received no antihypertensive drug, 6 (30%) one or two drugs and 4 (20%) more than two drugs. Gravidity of the three groups of patients was comparable (Table I). Gestational ages of the high and normal uric acid groups were similar, but that of the low-value group 2 weeks less. However, the differences were not significant. Systolic blood pressures were comparable, but diastolic values on admission were significantly higher in the high uric acid group than in the low-value group. In the high uric acid group 24 patients (96%) had 2+ or more proteinuria according to dipstick testing on admission to hospital. In the normal and low uric acid groups the figures were 158 (86%) and 14 (70%) respectively. The mean haematocrit on admission in the high uric acid group was 40%, in comparison with 36% in the low-value group ($P < 0.05$). Blood urea values on admission were significantly lower in the low uric acid group than in the other two groups. Creatinine clearance values were comparable and the admission-delivery periods almost identical (Table I).

Blood pressure before delivery in the high uric acid group was significantly lower than in the normal group (Table II). Haematocrit values were now more comparable, but urea values differed significantly between all three groups. Creatinine clearance levels were comparable.

Four, 22 and 7 patients in the high, normal and low uric acid groups respectively delivered before 28 weeks' gestation and their weight for gestational age could therefore not be assessed. Of the remaining patients 38%, 55% and 23% respectively of the different groups had small-for-gestational-age babies. The difference between the normal and low uric acid groups was statistically significant (Table III).

Birth weights at delivery were comparable between the high and normal uric acid groups, but significantly lower in the low-value group. However, gestational age at delivery in the low uric acid group was 2 weeks less than in the other two groups (Table II). Fetal reasons as an indication for delivery occurred more frequently in the low uric acid group. Perinatal mortality rates of the three groups ranged between 109 and 300. For babies who weighed 1 000 g or more at birth the perinatal mortality rates were 40, 11 and 50 per 1 000 for the high, normal and low uric acid values respectively (Table III).

Discussion

This study once again confirmed the findings of many previous studies that plasma urate values are increased in

Table I. Comparison between different uric acid values — admission data

	A. High uric acid (≥ 0.52 mmol/l; *N* = 25)	B. Normal uric acid (0.4 ± 0.11 mmol/l; *N* = 184)	C. Low uric acid (≤ 0.28 mmol/l; *N* = 20)	*P*-value
Age (yrs)				
Mean	27.0	26.0	26.8	NS
SD	6.8	6.0	6.8	
Median	25	25	26	
Primigravidas	24%	35%	30%	
Gravidity				
Mean	2.9	2.5	2.7	
SD	1.8	1.6	1.5	NS
Median	2	2	3	
Gestational age (wks)				
Mean	29.2	29.2	27.1	B/C $P < 0.05$†
SD	3.7	3.6	4.5	
Median	29	30	27	
SBP (mmHg)				
Mean	154	156	153	NS
SD	18	24	22	
Median	150	150	150	
DBP (mmHg)				
Mean	105	100	97	A/C $P < 0.05$*
SD	9	13	11	
Median	100	100	95	
Haematocrit (%)				
Mean	40	37	36	A/C $P < 0.05$†
SD	7	5	4	
Median	38	37	36	
Urea (mmol/l)				
Mean	4.4	4.0	3.1	A/C $P < 0.05$*
SD	1.2	1.5	1.1	B/C $P < 0.05$*
Median	4.4	3.7	3.2	
Creatinine clearance (ml/min)				
Mean	96	105	105	
SD	33	38	47	NS
Median	90	97	94	
Days before delivery				
Mean	11.8	13.3	13.0	
SD	7.7	12.2	8.3	NS
Median	11	11	12	

* Student's *t*-test.
† Mann-Whitney U-test.
SBP = Systolic blood pressure; DBP = diastolic blood pressure.

pre-eclampsia.[2,3] In addition, patients with a uric value of more than 1 SD above the mean had significantly higher diastolic blood pressures and haematocrit levels than patients with values of more than 1 SD below the mean. Blood urea values on admission were also higher in patients with high uric acid values. In this study the mean value was 0.4 ± 0.11 mmol/l. Although values of different laboratories cannot be compared directly, it is interesting to note that Redman *et al.*[3] regarded 0.24 mmol/l at 28 - 32 weeks and 0.36 mmol/l after 32 weeks as the upper levels of normal. As the use of antihypertensive drugs is associated with increased uric acid values,[13,14] it is possible that this medication might have had an effect in this study as only the last values were used for the analysis. As pre-eclampsia is usually a disease of the primigravida, it is interesting to note that only 24 - 35% of the different groups in this study were primigravidas. Patients with severe early pre-eclampsia are more likely to have an underlying medical disorder than those with disease of later onset.[15,16] The early onset of pre-eclampsia in our study and the small number of primigravidas involved, support the possibility of an underlying medical condition.

This study also confirms the association between uric acid values and intra-uterine growth retardation.[4-6] In the high uric acid group 38% of babies were growth retarded, as were 55% in the normal group. Significantly fewer small-for-gestational-age babies were born to mothers with uric acid levels 1 SD below the mean. This group also had the lowest blood pressure, haematocrit and blood urea values. It is therefore most likely that their pre-eclampsia was less severe.

Table II. Comparison between different uric acid values — data before delivery

	A. High uric acid (≥ 0.52 mmol/l; *N* = 25)	B. Normal uric acid (0.4 ± 0.11 mmol/l; *N* = 184)	C. Low uric acid (≤ 0.28 mmol/l; *N* = 20)	*P*-value
Gestational age (wks)				
Mean	30.8	31.1	28.7	
SD	3.8	3.3	4.2	NS
Median	30	32	29	
SBP (mmHg)				
Mean	142	153	150	A/B $P < 0.05$*
SD	18	22	28	
Median	140	150	140	
DBP (mmHg)				
Mean	90	97	96	A/B $P < 0.05$*
SD	9	13	18	
Median	90	100	90	
Haematocrit (%)				
Mean	38	36	34	
SD	6	5	8	NS
Median	39	37	34	
Urea (mmol/l)				
Mean	6.6	5.1	3.6	A/B $P < 0.005$†
SD	1.8	1.7	1.3	A/C $P < 0.005$†
Median	6.5	5.0	3.4	B/C $P < 0.005$†
Creatinine clearance (mmol)				
Mean	84	101	84	
SD	29	33	37	NS
Median	80	95	80	

* Student's *t*-test.
† Mann-Whitney U-test.

Table III. Neonatal outcome

	A. High uric acid (≥ 0.52 mmol/l; *N* = 25)	B. Normal uric acid (0.4 ± 0.11 mmol/l; *N* = 184)	C. Low uric acid (≤ 0.28 mmol/l; *N* = 20)	*P*-value
Birth weight (g)				
Mean	1 400	1 357	1 100	B/C $P < 0.05$*
SD	548	516	535	
Median	1 447	1 315	1 088	B/C $P < 0.05$†
SGA	38%	55%	23%	
Indications for delivery				
Maternal	12	94	7	
Fetal	6	48	7	
Maternal and fetal	6	30	3	
Spontaneous onset	0	3	0	
Induction for IUD	1	6	2	
Induction after 34 weeks	0	3	1	
Caesarean sections	72%	66%	60%	
Perinatal outcome				
Alive	18	145	11	
Abortion (< 500 g)	0	7	2	
IUD	3	11	4	
All NND	4	21	3	
PNM rate	200 (5/25)	109 (20/184)	300 (6/20)	
PNM rate (birth weight ≥ 1 000 g)	40 (1/25)	11 (2/184)	50 (1/20)	

* Student's *t*-test.
† Fisher's exact test.
IUD = intra-uterine death; NND = neonatal death; PNM = perinatal mortality (only neonatal deaths within 7 days considered); SGA = small for gestational age.

With regard to blood pressure values before delivery, it is interesting to note that better control was achieved in the high uric acid group, but it was also this group that showed the greatest increase in blood urea values.

Patients in the low uric acid group were admitted to hospital about 2 weeks earlier than those in the other groups and were delivered about 14 days earlier. This group's babies therefore weighed significantly less at delivery. In contrast to the other two groups, fetal indications for delivery occurred more frequently in the low uric acid group. The reasons for this are uncertain. Because of the small number of patients in this group and the earlier delivery, comparison of their perinatal mortality rate with those of the other two groups will, to a certain extent, be biased.

The fact that the perinatal mortality rate was not higher in the high uric acid group, in spite of higher initial diastolic blood pressure and blood urea values, calls into question the belief that raised uric acid values are associated with more perinatal deaths. Better control of blood pressure was obtained in the high uric acid group. This also demonstrates that tight control of blood pressure with several drugs is not associated with more perinatal deaths.

As this study could not confirm the association between more perinatal deaths and high uric acid values, we advise that uric acid values *per se* should not influence one's decision to deliver patients with early severe pre-eclampsia. The decision to deliver should be individualised for different patients, with the maternal and fetal dangers carefully balanced against one another.

We wish to thank the MRC for financial support and our research nurse, Erna Carstens, for her hard and precise work.

REFERENCES

1. Redman CWG, Willliams GF, Jones DD, Wilkinson RH. Plasma urate and serum deoxycytidylate deaminase measurements for the early diagnosis of preeclampsia. *Br J Obstet Gynaecol* 1977: **84:** 904-908.
2. Dunlop W, Davison JM. The effect of normal pregnancy upon the renal handling of uric acid. *Br J Obstet Gynaecol* 1977; **84:** 13-21.
3. Redman CWG, Beilin LJ, Bonnar J, Wilkinson RH. Plasma-urate measurements in predicting fetal death in hypertensive pregnancy. *Lancet* 1976; **2:** 1370-1373.
4. Varma TR. Serum uric acid levels as an index of fetal prognosis in pregnancies complicated by pre-existing hypertension and pre-eclampsia of pregnancy. *Int J Gynaecol Obstet* 1982; **20:** 401-408.
5. Schuster E, Weppelmann B. Plasma urate measurements and fetal outcome in preeclampsia. *Gynecol Obstet Invest* 1981; **12:** 162-167.
6. Sagen N, Haram K, Nilsen ST. Serum urate as a predictor of fetal outcome in severe pre-eclampsia. *Acta Obstet Gynecol Scand* 1984; **63:** 71-75.
7. Yoshimura A, Ideura T, Iwasaki S, Koshikawa S. Significance of uric acid clearance in pre-eclampsia. *Am J Obstet Gynecol* 1990; **162:** 1639-1640.
8. Odendaal HJ, Pattinson RC, Du Toit R, Grové D. Frequent fetal heart rate monitoring for early detection of abruptio placentae in severe proteinuric hypertension. *S Afr Med J* 1988; **74:** 19-21.
9. Odendaal HJ, Pattinson RC, Du Toit R. Fetal and neonatal outcome in patients with severe pre-eclampsia before 34 weeks. *S Afr Med J* 1987; **71:** 555-558.
10. Odendaal HJ, Pattinson RC, Bam R, Grové D, Kotze TJvW. Aggressive or expectant management for patients with severe pre-eclampsia between 28 - 34 weeks' gestation: a randomised controlled trial. *Obstet Gynecol* 1990; **76:** 1070-1075.
11. Odendaal HJ, Steyn DW, Norman K, Kirsten GF, Smith J, Theron GB. Improved perinatal mortality rates in 1001 patients with severe pre-eclampsia. *S Afr Med J* 1995; **85:** 1071-1076.
12. Theron GB, Thompson ML. A centile chart for an urban population of the Western Cape. *S Afr Med J* 1995; **85:** 1289-1292.
13. Sibai BM, Anderson GD, McCubbin JH. Eclampsia II. Clinical significance of laboratory findings. *Obstet Gynecol* 1982; **59:** 153-157.
14. Dekker GA, Sibai BM. Early detection of preeclampsia. *Am J Obstet Gynecol* 1991; **165:** 160-172.
15. Pattinson RC, Odendaal HJ, Du Toit R. Conservative management of severe proteinuric hypertension before 28 weeks' gestation. *S Afr Med J* 1988; **73:** 516-518.
16. Sibai BM, Mercer B, Sarinoglu C. Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis. *Am J Obstet Gynecol* 1991; **165:** 1408-1412.

Accepted 30 Aug 1995.