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Original article

Haematological and biochemical profile of uncomplicated pregnancy in nulliparous women; a longitudinal study

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Abstract

Background: Most laboratory parameters change during pregnancy. A serial study of a large number of routine haematological and biochemical blood parameters and biochemical urine parameters was conducted in a group of 66 healthy nulliparous pregnant women, who had an uncomplicated pregnancy.

Methods: Blood samples and 24-h urine samples were obtained at four weeks intervals during pregnancy and at 1 (1P) and 6 (6P) weeks after delivery.

Results: During pregnancy, haemoglobin concentration, haematocrit and erythrocyte count were lower, mean cell volume was not different, and mean cell haemoglobin and mean cell haemoglobin concentration were enhanced. The platelet count during pregnancy was not different from the level at 6P but increased 60% at 1P. Serum ferritin decreased 50% whereas plasma fibrinogen increased 100%. Serum creatinine (–28%), uric acid (–35%) and urea (–40%) concentrations were reduced during pregnancy. The serum concentrations of sodium (–4 mmol/l) and potassium (–0.2 mmol/l) were lower, but serum chloride was unaltered. Serum protein and albumen concentrations declined by 7.8 and 9.4 g/l respectively. The serum concentrations of bilirubin, ALAT, ASAT and γ -GT remained unaltered. Serum LDH was 30% above normal non-pregnant values at 1P. The heat-stable alkaline phosphatase level increased in the third trimester. Heat-stable and heat-labile fractions were both elevated at 1P. The serum osmolality was 9 mosmol/kg lower and urine volume was about 25% higher during pregnancy. The creatinine excretion was unaltered but creatinine clearance increased by 25%.

Conclusions: The concentrations of most components change during pregnancy. The interpretation of results of laboratory tests in pregnant women should be made with caution.

Keywords: Laboratory parameters; Uncomplicated pregnancy

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1. Introduction

Successful outcome of pregnancy requires a large number of rather dramatic physiological adaptations. These adaptations involve changes of the metabolism in most organ systems, resulting in changes in the biochemical composition of the blood. In order to be able to interpret laboratory parameters of pregnant women, physicians (next to obstetricians) caring for those women have to be aware of these physiological changes that accompany normal pregnancy. In the literature, little attention has been paid to the gestational changes in electrolytes and other biochemical components of the serum and haematological parameters of the blood in normal human pregnancy. Moreover, the scarce literature available is inconclusive for several reasons; many studies were cross-sectional, the populations studied included both nulliparous and multiparous women, and pregnancies complicated by pathological conditions were not excluded.

In a longitudinal study we simultaneously studied a large number of haematological and biochemical blood parameters and the urinary excretion of electrolytes and creatinine. As adaptation to pregnancy might change with increasing parity [1] and may well be different in abnormal pregnancy, our study population was limited to healthy nulliparous pregnant women delivering at term a healthy and appropriate-for-gestational-age infant after an uncomplicated pregnancy. The results of the present study are compared with the available longitudinal studies.

2. Materials and methods

Study population

The study protocol was approved by the local ethics committee of the University Hospital. Ninety-eight healthy nulliparous pregnant women were included in the study after informed consent had been obtained. All pregnancies were singleton and accurately dated by the last menstrual period, pregnancy test and one or two ultrasound investigations before the 12th gestational week. After the last check-up at 6 weeks after delivery,

Table 1

Criteria for uncomplicated singleton pregnancy

Delivery \geq day 259 and \leq day 294 of gestation
Birth weight \geq 10th centile and \leq 90th centile
Blood pressure $<$ 90 mmHg throughout pregnancy
No proteinuria (\leq 300 mg/24 h)
No dietary restrictions in pregnancy
No medication except for iron and vitamin supplements

each pregnancy was classified as having been complicated or uncomplicated. Uncomplicated pregnancy was defined according to the criteria listed in Table 1. Only the data of the pregnancies classified as uncomplicated were used in this analysis. According to those criteria, a total of 32 women were excluded from evaluation for reasons of developing gestational hypertension (according to the criteria of Davey and MacGillivray, 1988) [2] ($n = 16$), low birth weight ($<$ 10th percentile, $n = 9$) [3], high birth weight ($>$ 90th percentile, $n = 6$), premature delivery ($<$ 37 weeks, $n = 8$) or postmature delivery ($>$ 42 weeks, $n = 1$). Thus 66 women could be evaluated further. None of the participants has been hospitalized for severe morning sickness. The group characteristics are summarized in Table 2. Since most women in our hospital receive oral iron supplements during pregnancy, we decided to supplement all women from the 20th week until delivery to keep the group homogeneous. Some women also used folate supplements. Some data from 20 women contributed to three previous studies [4–6].

Study protocol

The studies were performed between 13.00 and 17.00 hours. Each individual patient was seen

Table 2

Group characteristics of 66 women with uncomplicated pregnancy

	Median	(min–max)
Age (yr)	28.0	(21.2–35.6)
Duration of pregnancy (days)	279	(259–293)
Birth weight (g)	3185	(2630–3915)
Percentile birth weight	40	(10–85)
Vaginal blood loss after delivery (ml)	400	(150–1300)

at approximately the same time of day for each visit during pregnancy and after delivery.

After an obstetric check-up, blood pressure was measured twice, in the sitting position with an automatic device, which uses the oscillometric principle (Dinamap). Afterwards, blood samples were taken from an antecubital vein, after the patient had rested for 20 minutes in the left lateral tilt position. Patients were asked to refrain from eating, drinking coffee and smoking during the last hour before venipuncture. In addition, 24-h urine samples were collected the day before each outpatient clinic visit.

Serial measurements were made in weeks 12, 16, 20, 24, 28, 32, 36, and 38 of pregnancy and at

1 (1P) and 6 (6P) weeks after delivery. The parameters concerned, the methods of analysis and reference values for non-pregnant women are listed in Table 3. The creatinine clearance was calculated. To correct for possible incomplete collection of 24-h urine samples, the urinary excretions of the electrolytes are presented both as excretion in mmol/24 h and as a ratio of the electrolyte and creatinine (mmol/mmol) in the 24-h samples. Furthermore, the electrolyte-free water clearance (EFWC) was calculated as follows:

EFWC

$$= U_{\text{vol}} \times [1 - \{(U_{[\text{sodium}]} + U_{[\text{potassium}]}) / S_{[\text{sodium}]}\}]$$

Table 3
Laboratory techniques and reference values for non-pregnant women from our laboratory

Compound	Material	Analytical method	Reference value
Haemoglobin (Hb)	EDTA blood	Cyanide method	7.3–9.7 mmol/l
Haematocrit (Ht)	EDTA blood	derived	0.34–0.46 L/l
Erythrocyte count	EDTA blood	direct count	$3.7\text{--}5.2 \times 10^{12}/\text{l}$
Mean cell volume (MCV)	EDTA blood	direct measurement	80–96 fL
Mean cell haemoglobin (MCH)	EDTA blood	derived	1600–2000 amol
Mean cell haemoglobin concentration (MCHC)	EDTA blood	derived	18.5–22.5 mmol/l
Thrombocyte count	EDTA blood	direct count	$150\text{--}350 \times 10^9/\text{l}$
Fibrinogen	citrate plasma	Clauss	1.6–3.2 g/l
Ferritin	serum	IEMA (Tandem-E-Fer, Hybritech)	15–350 $\mu\text{g}/\text{l}$
Creatinine	serum	Jaffé	50–90 $\mu\text{mol}/\text{l}$
Uric acid	serum	Uricase/catalase reaction	0.15–0.40 mmol/l
Urea	serum	Urease method	3.0–7.0 mmol/l
Sodium	serum	Indirect potentiometry	137–144 mmol/l
Potassium	serum	Indirect potentiometry	3.4–4.6 mmol/l
Chloride	serum	Indirect potentiometry	98–107 mmol/l
Protein	serum	Biuret	60–80 g/l
Albumen	serum	Bromocresol green	40–55 g/l
Bilirubin	serum	Caffeine/sodium-benzoate at 30°C	< 10 $\mu\text{mol}/\text{l}$
ALAT	serum	L-Alanine and 2-oxoglutarate at 30°C [8]	< 30 IU/l
ASAT	serum	L-Aspartate and 2-oxoglutarate at 30°C [9]	< 25 IU/l
LDH	serum	Pyruvate at 30°C [10]	< 330 IU/l
γ -GT	serum	L- γ -Glutamyl-3-carboxy-4-nitroanilide at 30°C [11]	< 35 IU/l
Alkaline phosphatase	serum	p-Nitrophenylphosphate at 30°C [12]	< 120 IU/l
Osmolality	serum	Freezing point osmometry	280–300 mosmol/kg
Sodium	urine	Flame photometry	
Potassium	urine	Flame photometry	
Chloride	urine	Chlorocounter	
Creatinine	urine	Jaffé	
Osmolality	urine	Freezing point osmometry	

where U_{vol} is the 24-h urine volume, $U_{[\text{sodium}]}$ and $U_{[\text{potassium}]}$ are the urinary concentrations of sodium and potassium respectively, and $S_{[\text{sodium}]}$ is the serum sodium concentration [7]. Bilirubin concentration, the liver enzyme concentrations and ferritin levels were measured in weeks 12, 32, 1P and 6P.

In the last 23 women of the study population, the osmolality of the serum (S_{osmol}) and the urine (U_{osmol}) was determined. The excretion of solutes was calculated by multiplying urine volume with the urine osmolality. In addition, the free-water clearance (FWC) was calculated according to the following equation:

$$\text{FWC} = U_{\text{vol}} \times [1 - (U_{\text{osmol}}/S_{\text{osmol}})].$$

Statistical analysis

Changes in all parameters studied in comparison with values at 6 weeks after delivery (6P) were tested with the Wilcoxon matched-pairs signed rank test. The level of statistical significance for each comparison was taken to be $0.10/k$ (k = number of comparisons). The total maximum type I error is then 0.10. Due to the interdependence of the values at the subsequent time points, the overall type I error is probably nearer to 5% than to 10%. The results are presented in box and whisker plots. The upper and the lower limits of the box display the 75th and 25th centiles, the line in between is the median, and the lower and upper whiskers respectively indicate the 5th and 95th centiles of the distribution. Values below the 5th centile and above the 95th centile are indicated as points outside the whiskers.

3. Results

The laboratory parameters in pregnancy were compared with control values at 6 weeks after delivery in the same group of women. At 6 weeks

after delivery, the values of most parameters were within the normal non-pregnant range. The serum ferritin concentration at 6P, however, was below the normal non-pregnant range.

Haematological data (Fig. 1)

The median Hb, Ht and erythrocyte count were lower throughout pregnancy compared with the median levels at 6 weeks post partum (6P). A nadir was demonstrated in week 28. The maximum differences in week 28 compared with week 6P for Hb, Ht and erythrocyte count were -0.9 mmol/l (-12%), -0.05 l/l (-13%) and -0.7×10^{12} cells/l (-17%) respectively. MCV during pregnancy did not differ significantly from the 6P value. In the course of pregnancy, however, the median MCV increased from 90 at week 12 up to 91–94 between weeks 20 and 38. MCH and MCHC were significantly elevated throughout pregnancy as compared with the postpartum values. Within pregnancy, no large changes were observed.

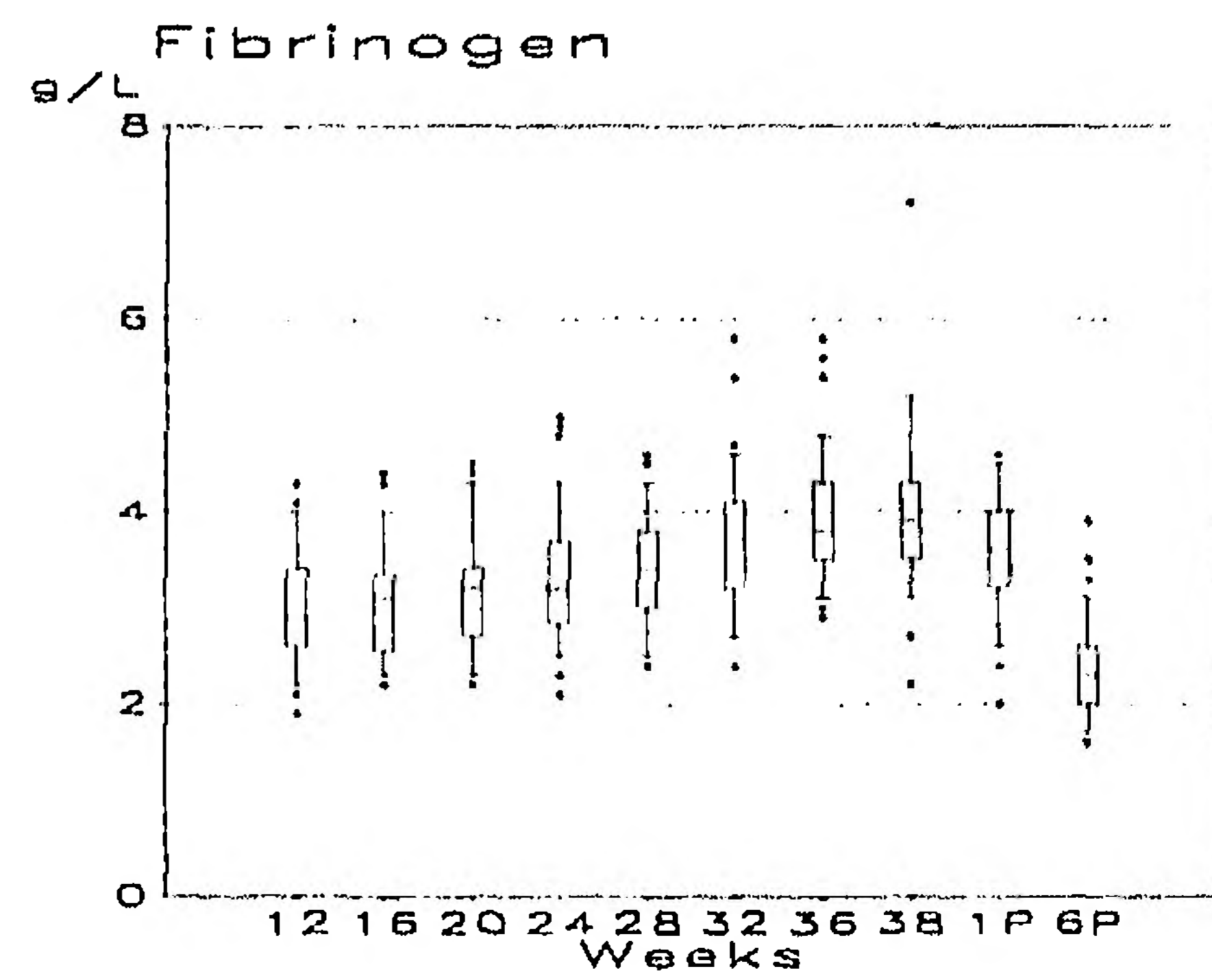
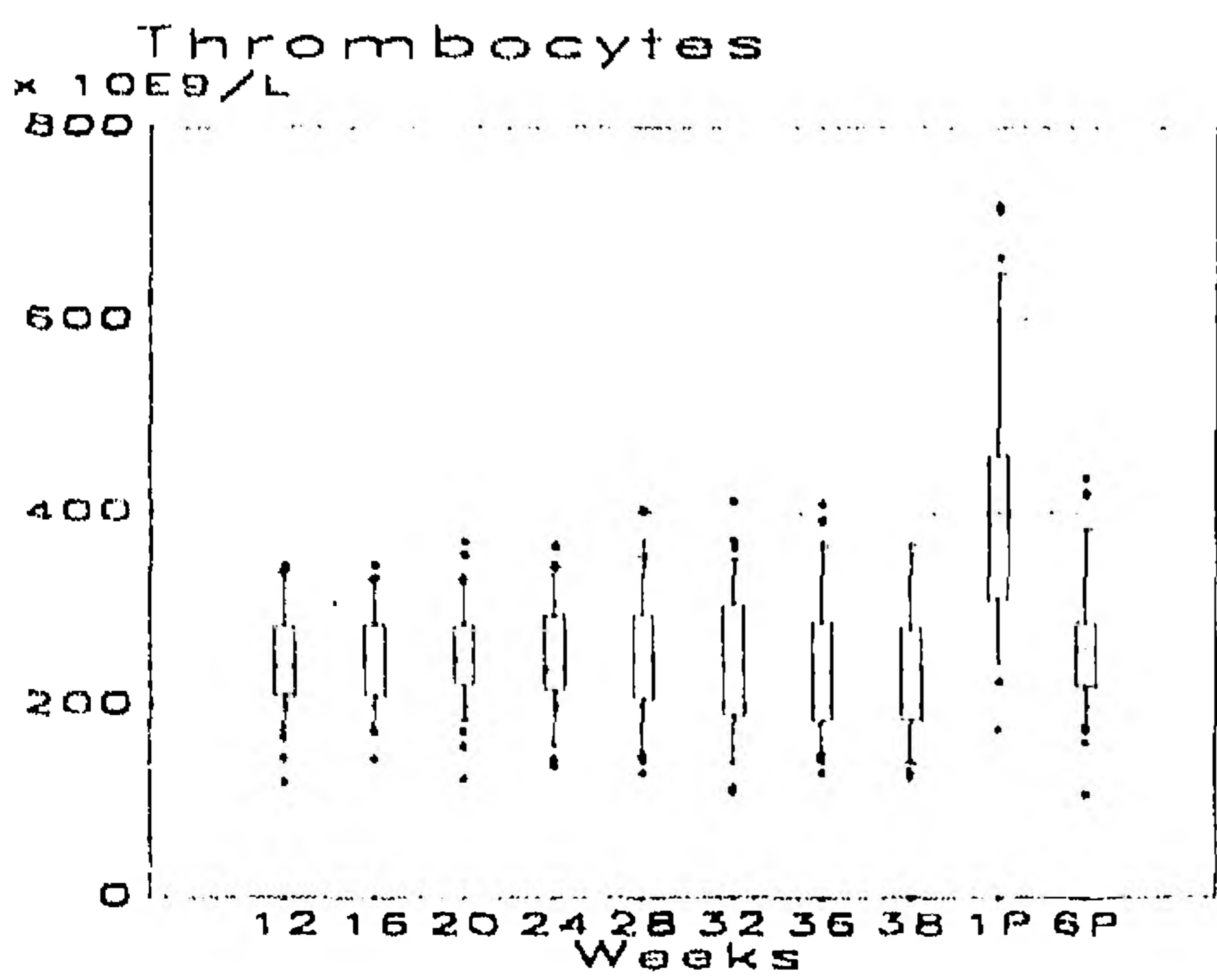
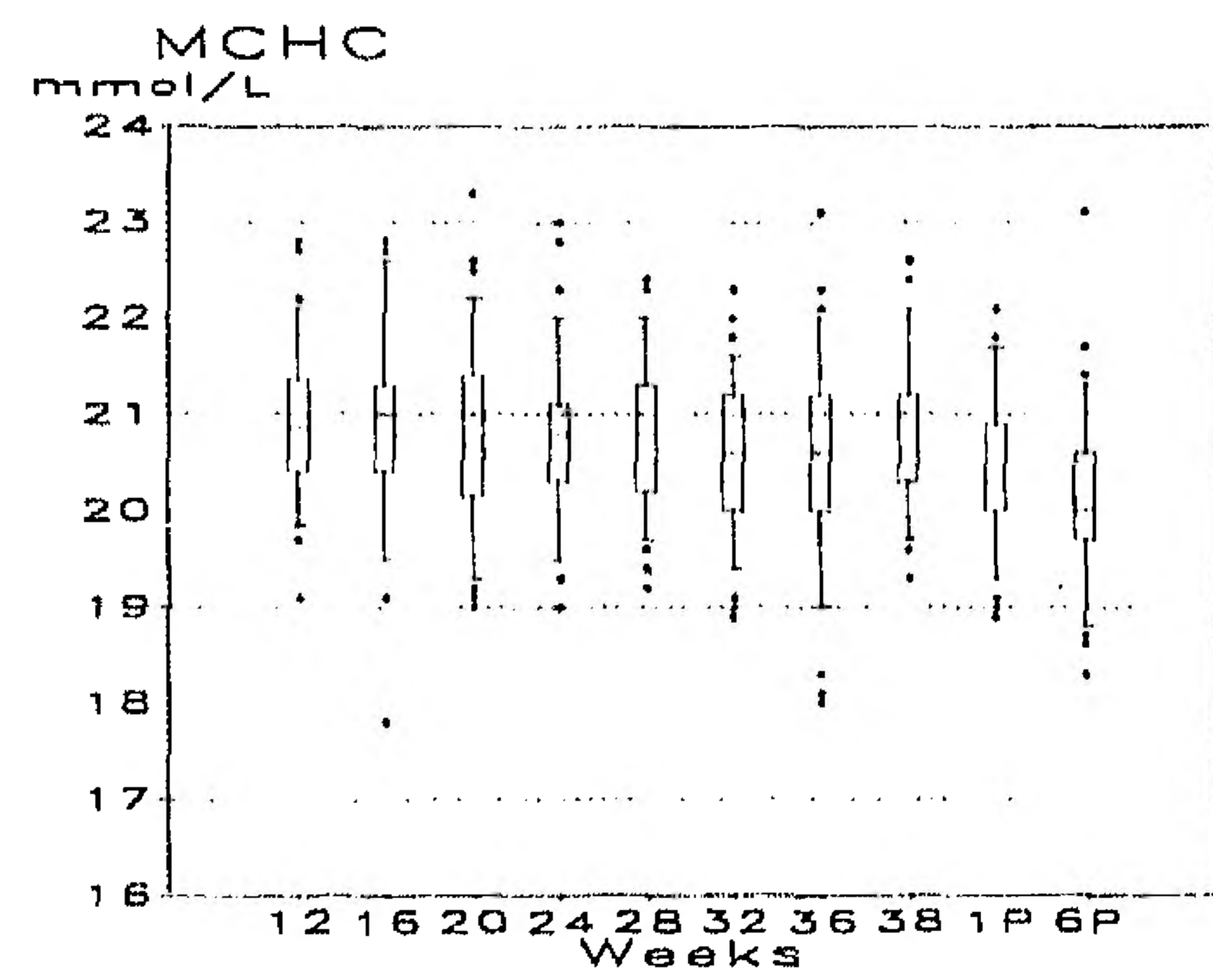
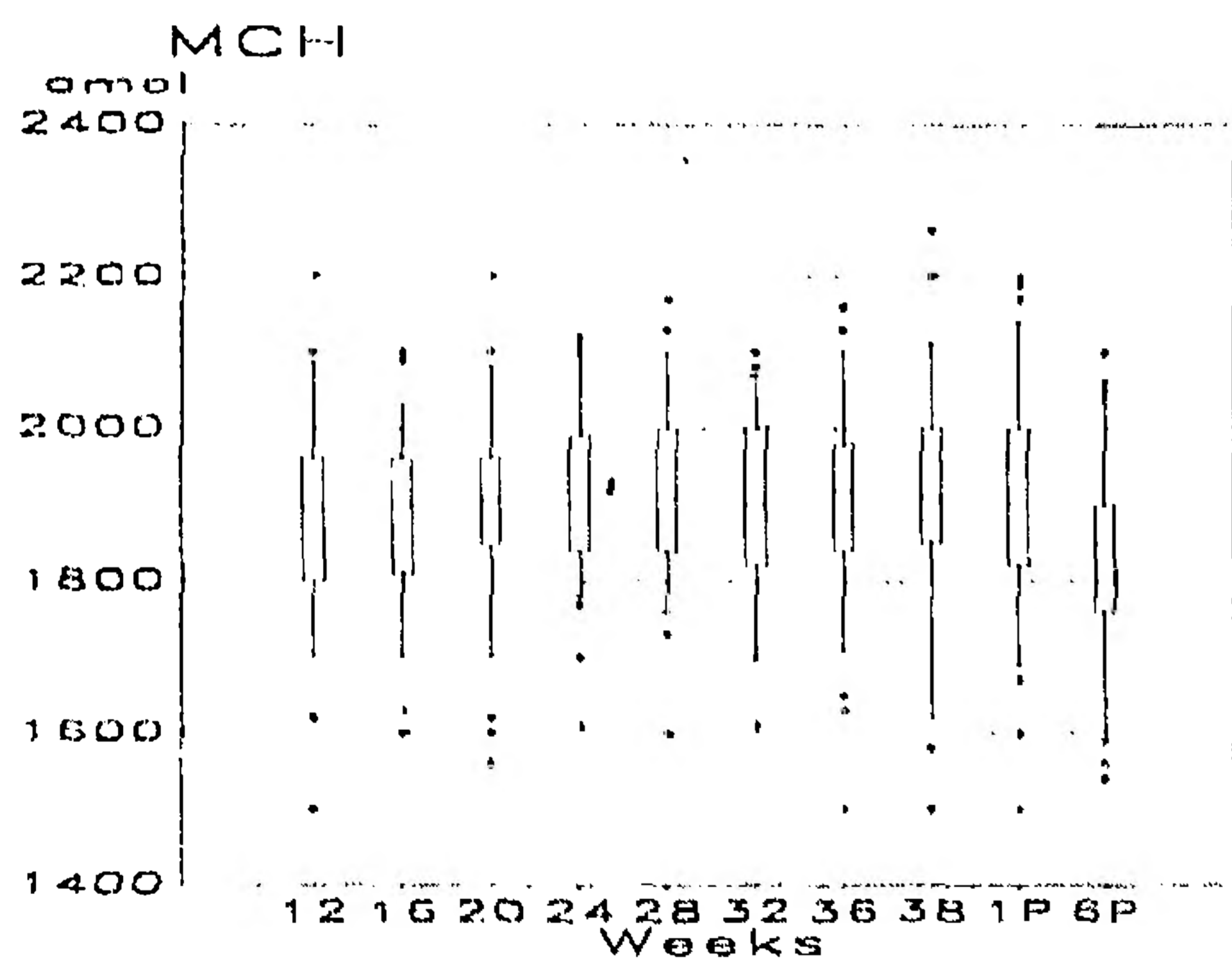
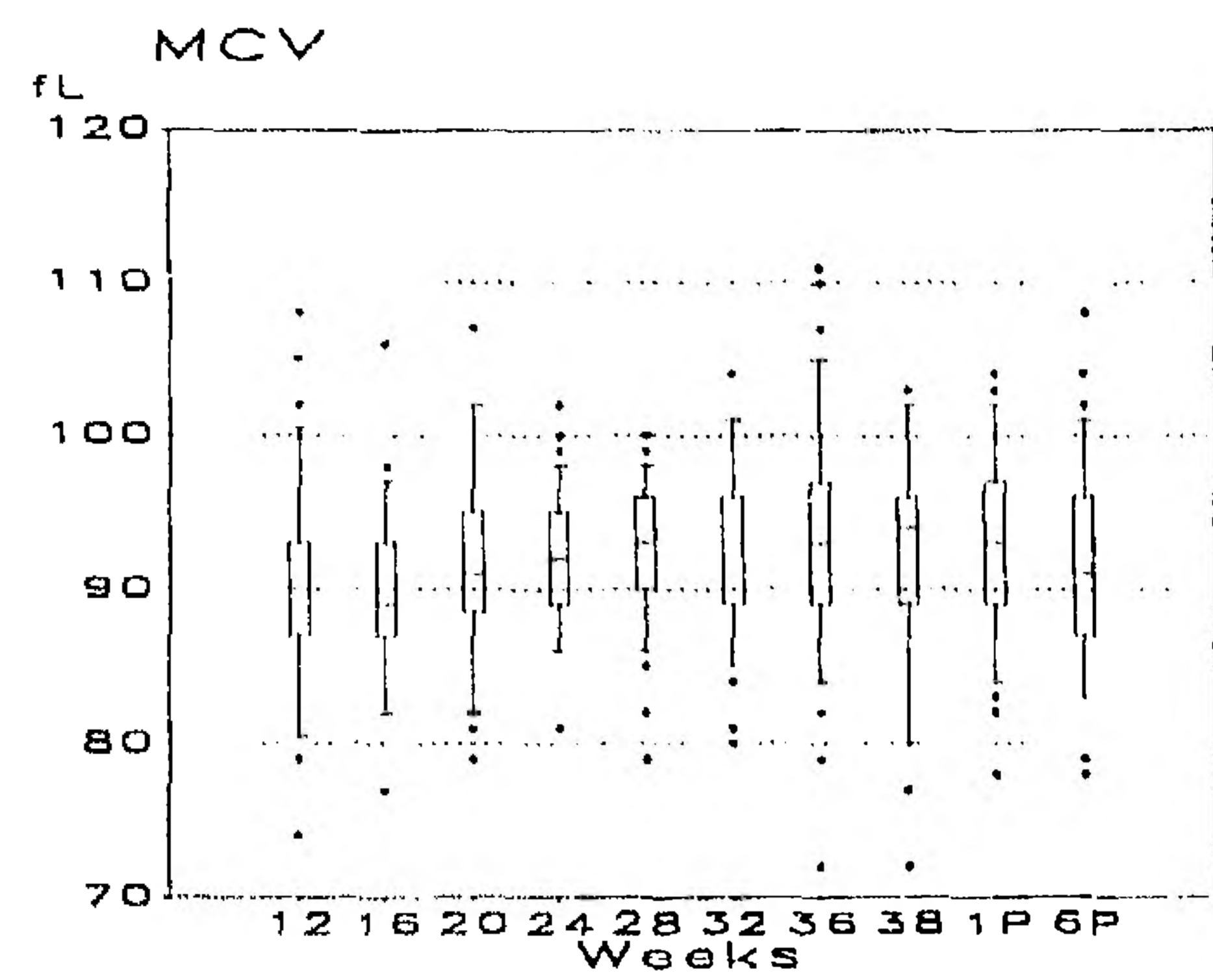
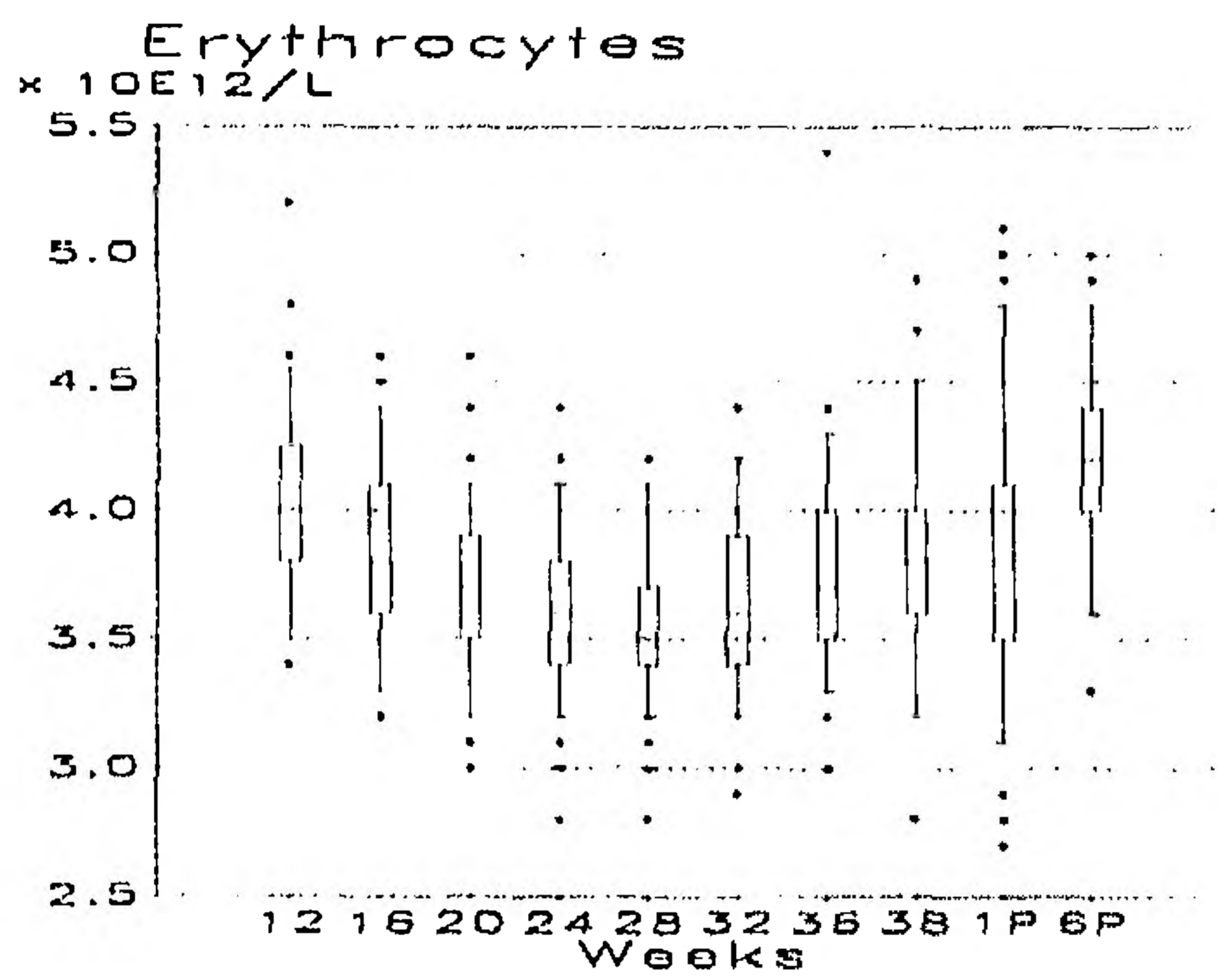
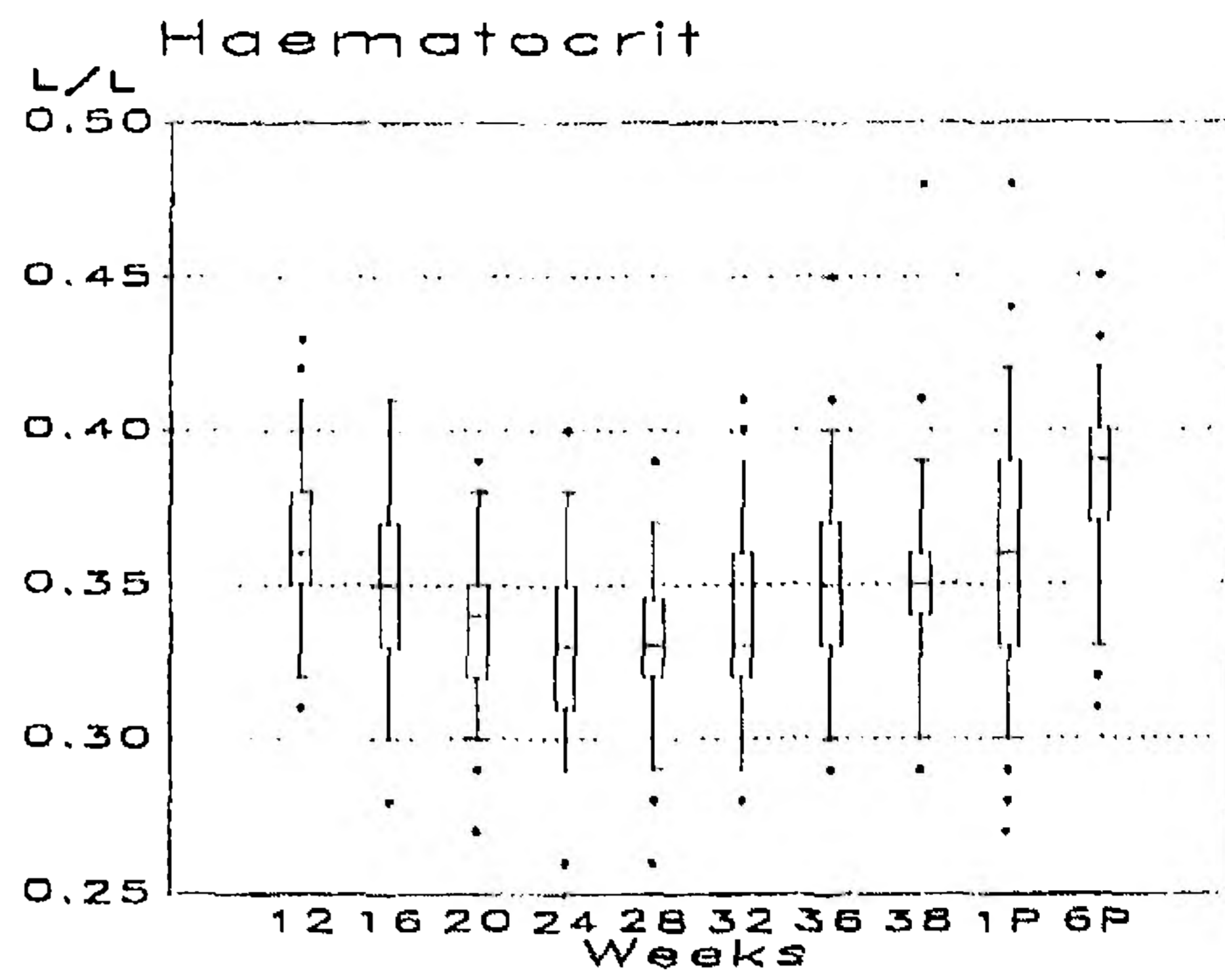
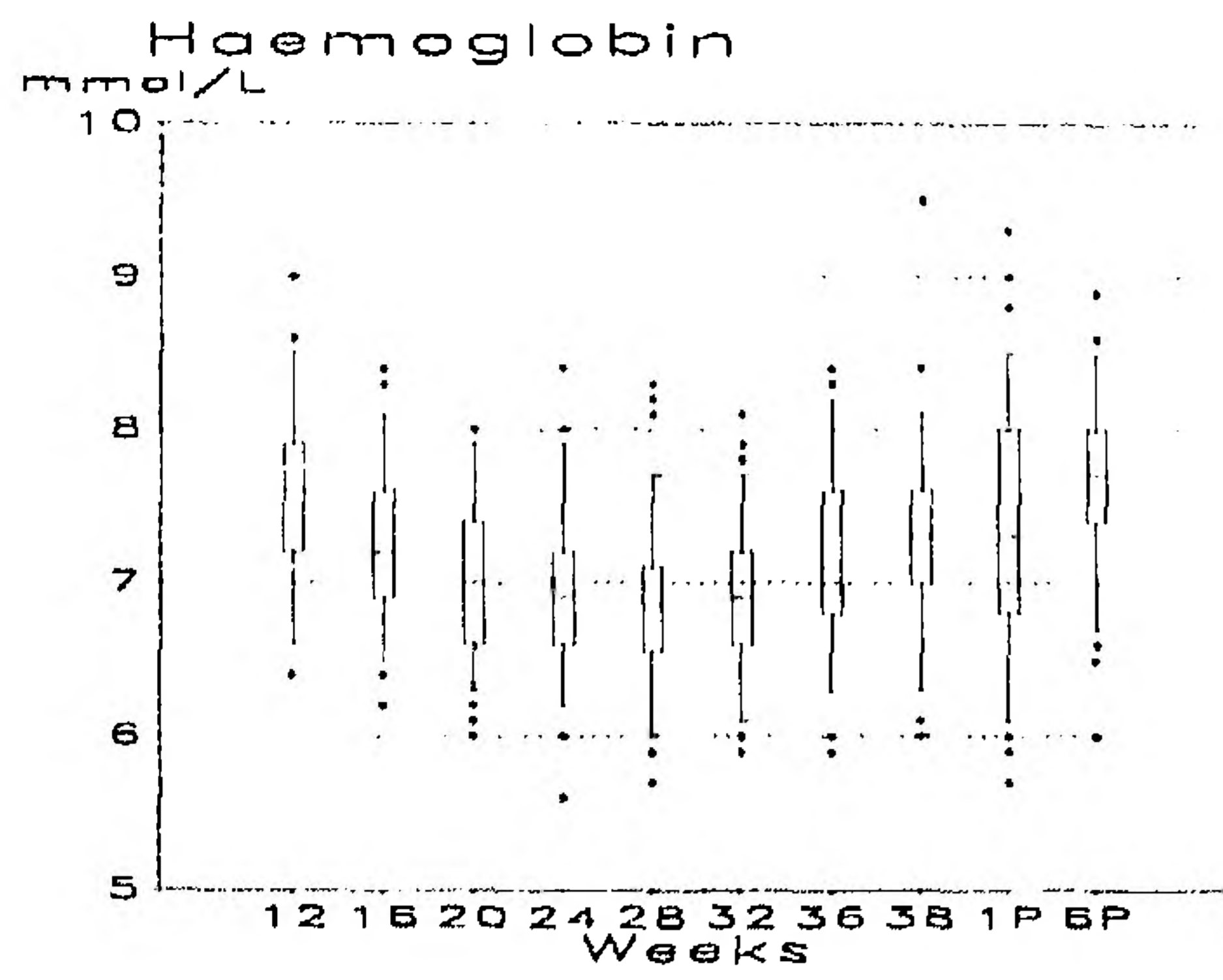
The platelet count did not show major changes throughout pregnancy and was not different from 6P. At 1 week after delivery (1P), however, the platelet count was significantly higher than at 6P, with median values of 387 and 259×10^9 /l, respectively. The fibrinogen concentration in week 12 of pregnancy was about 10% higher than at 6P and throughout pregnancy this difference increased to about 50% in late gestation.

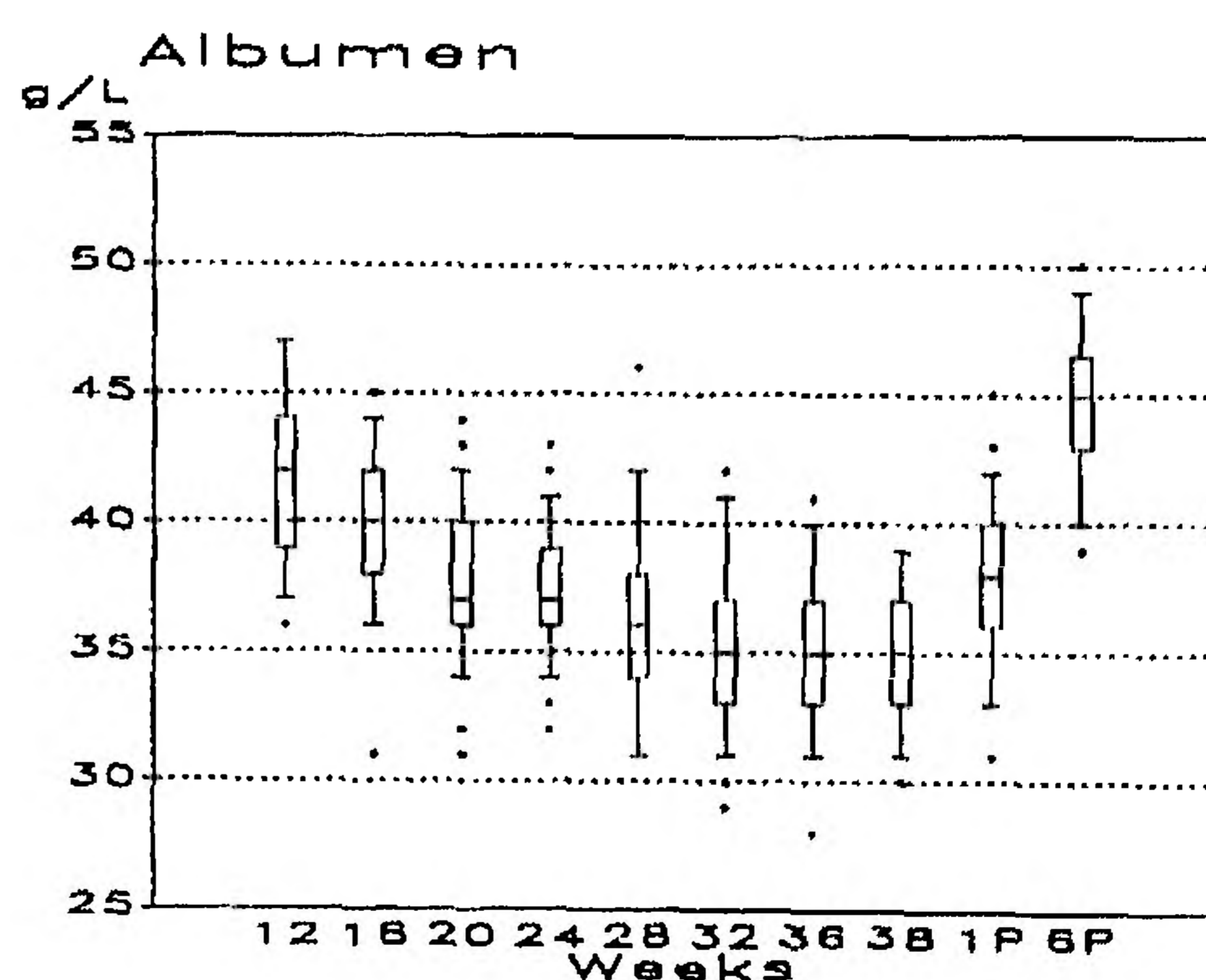
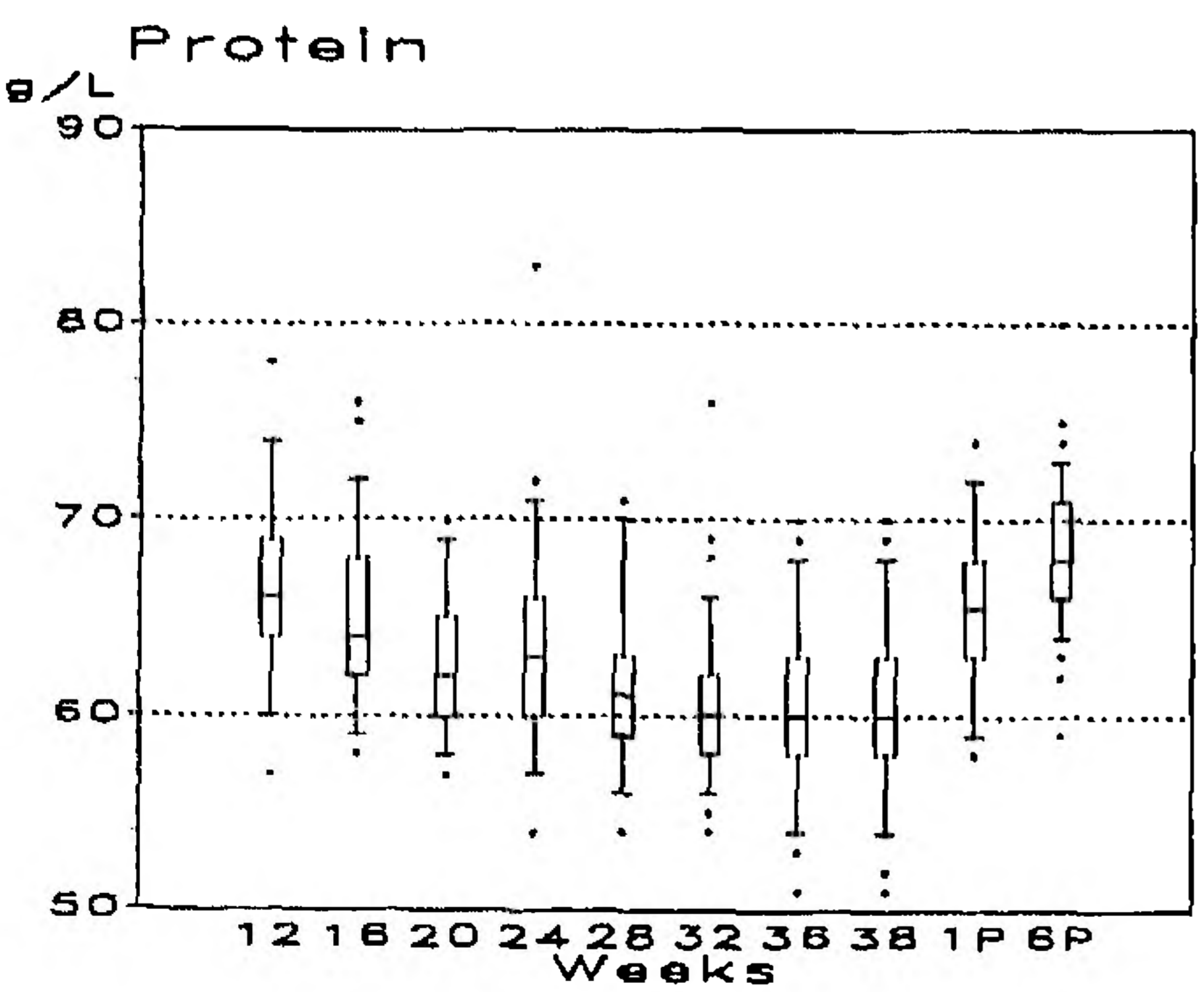
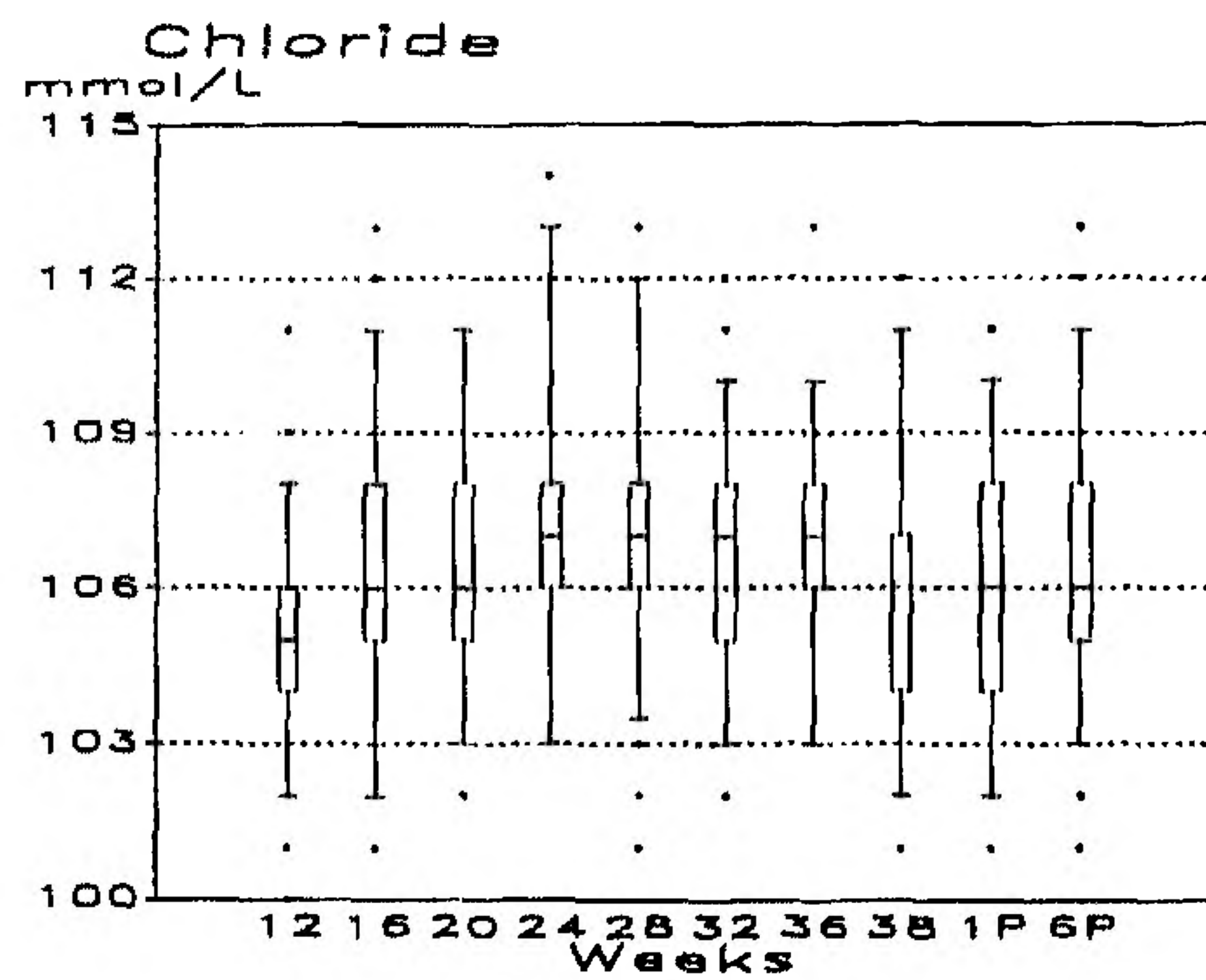
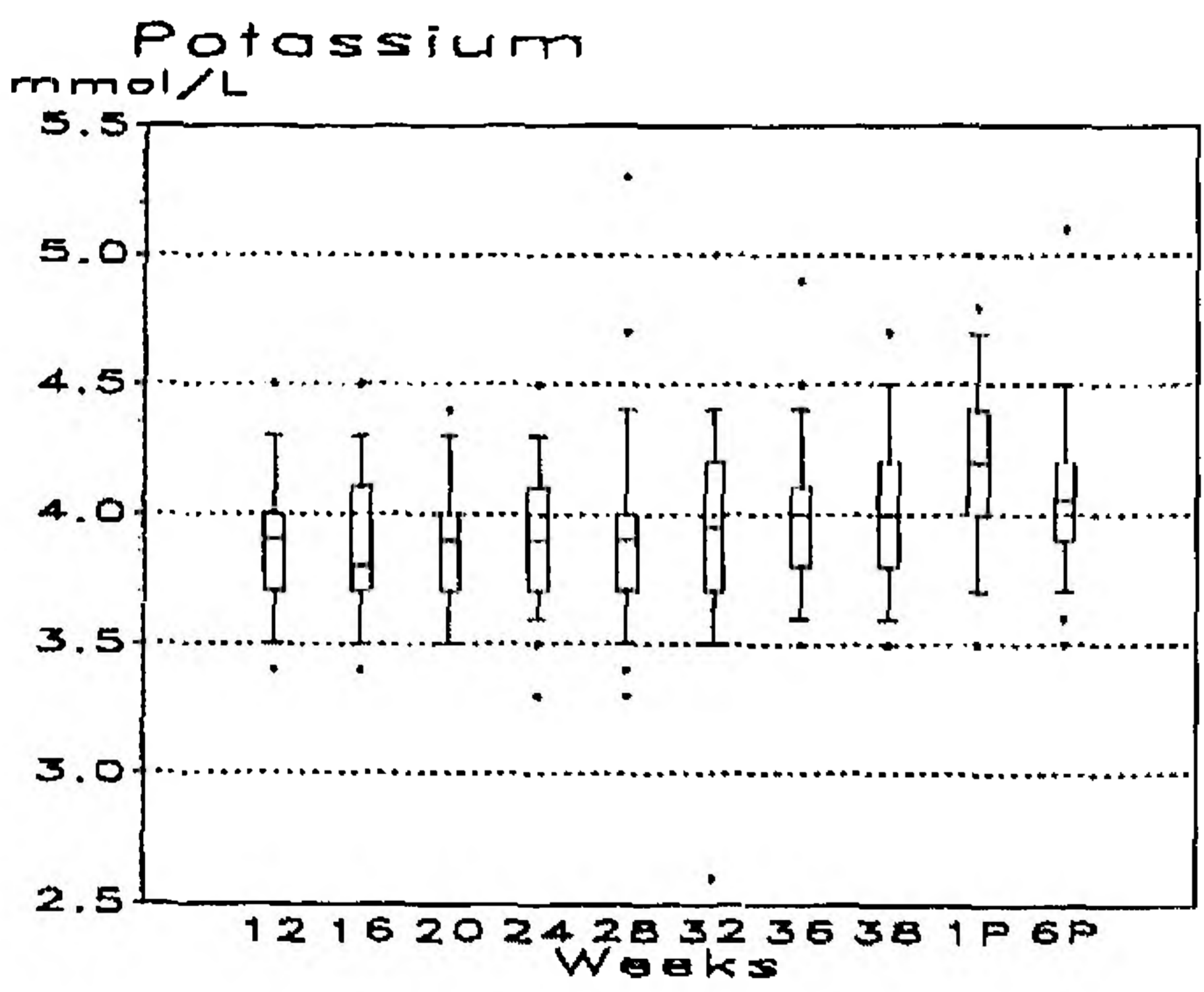
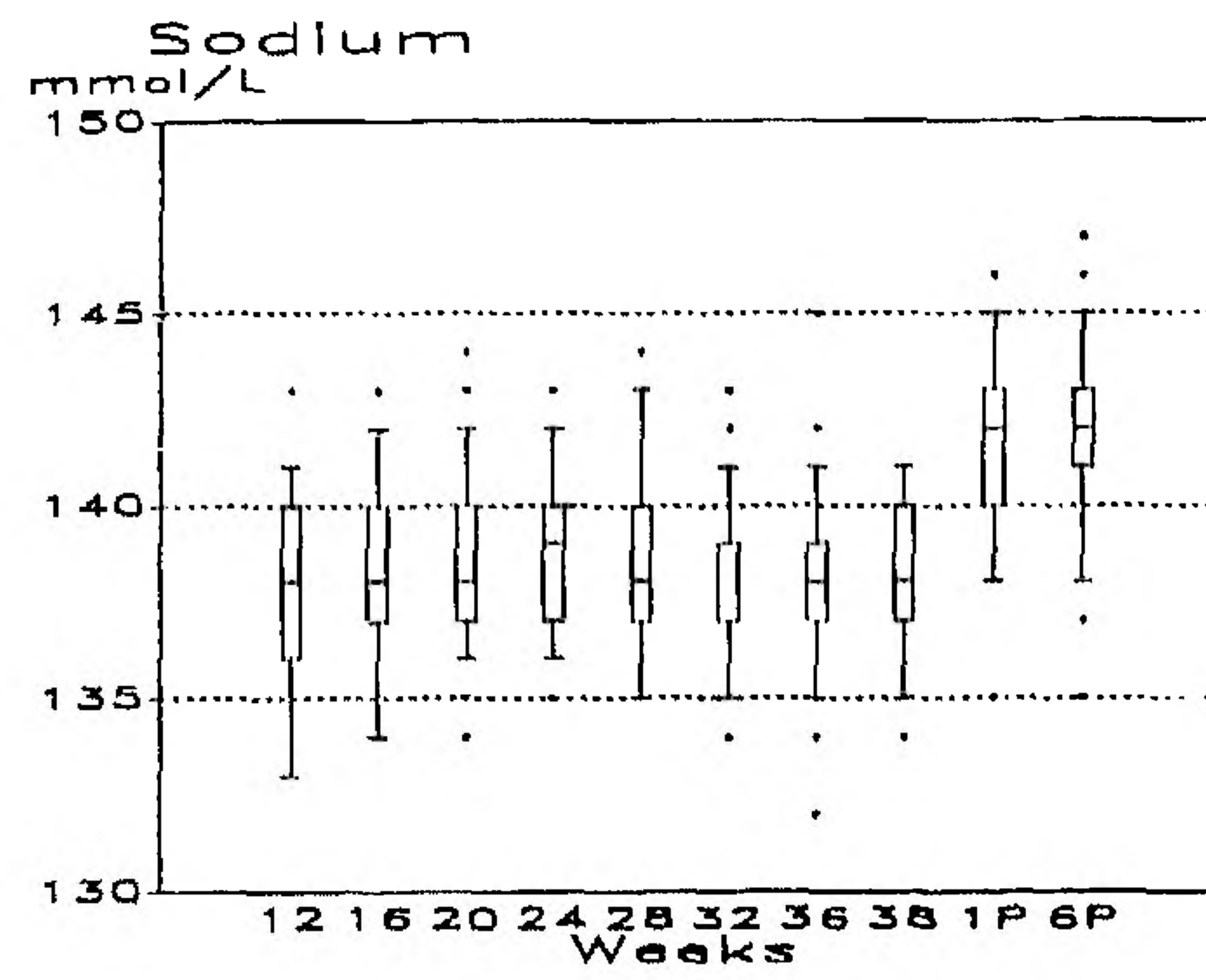
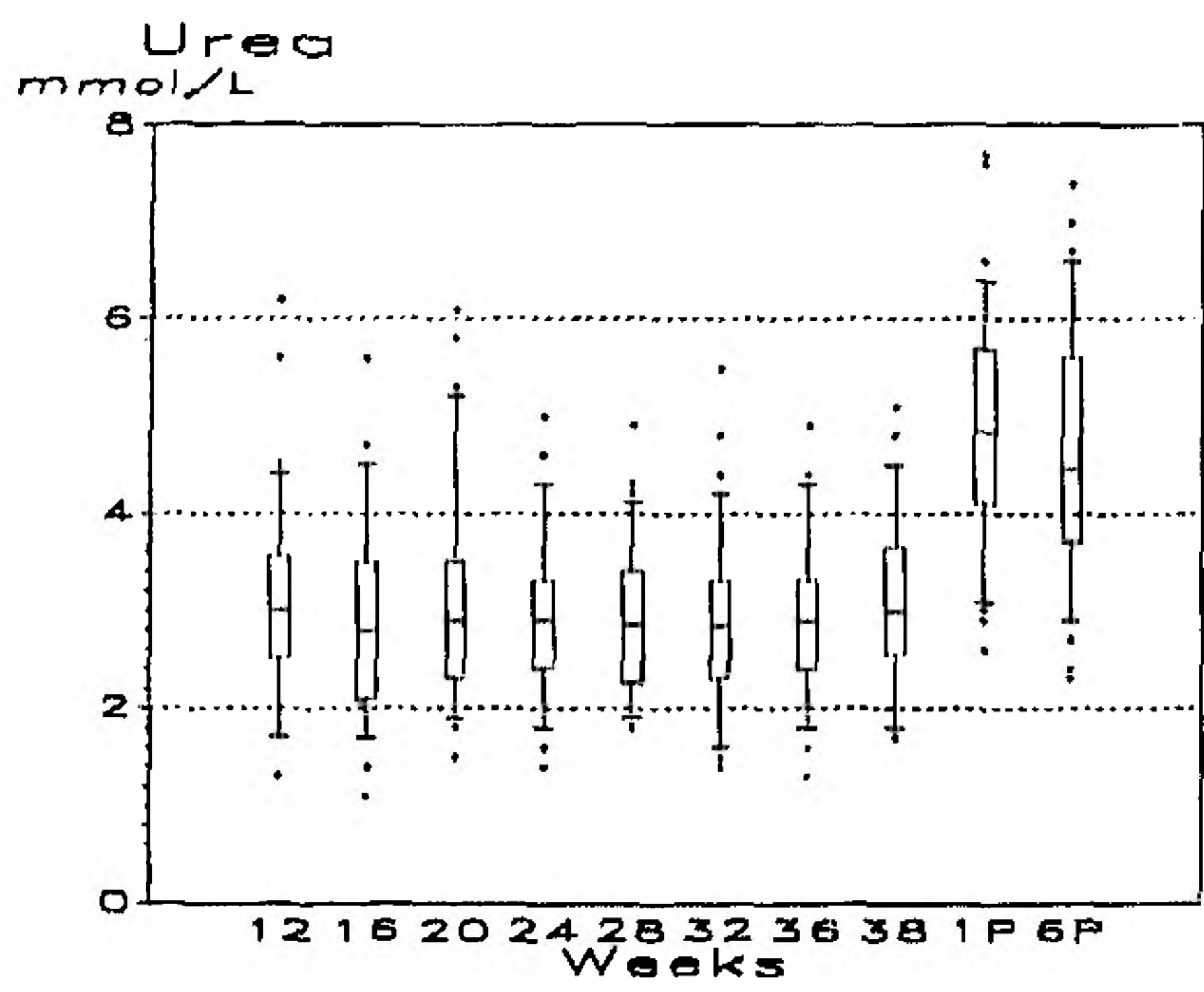
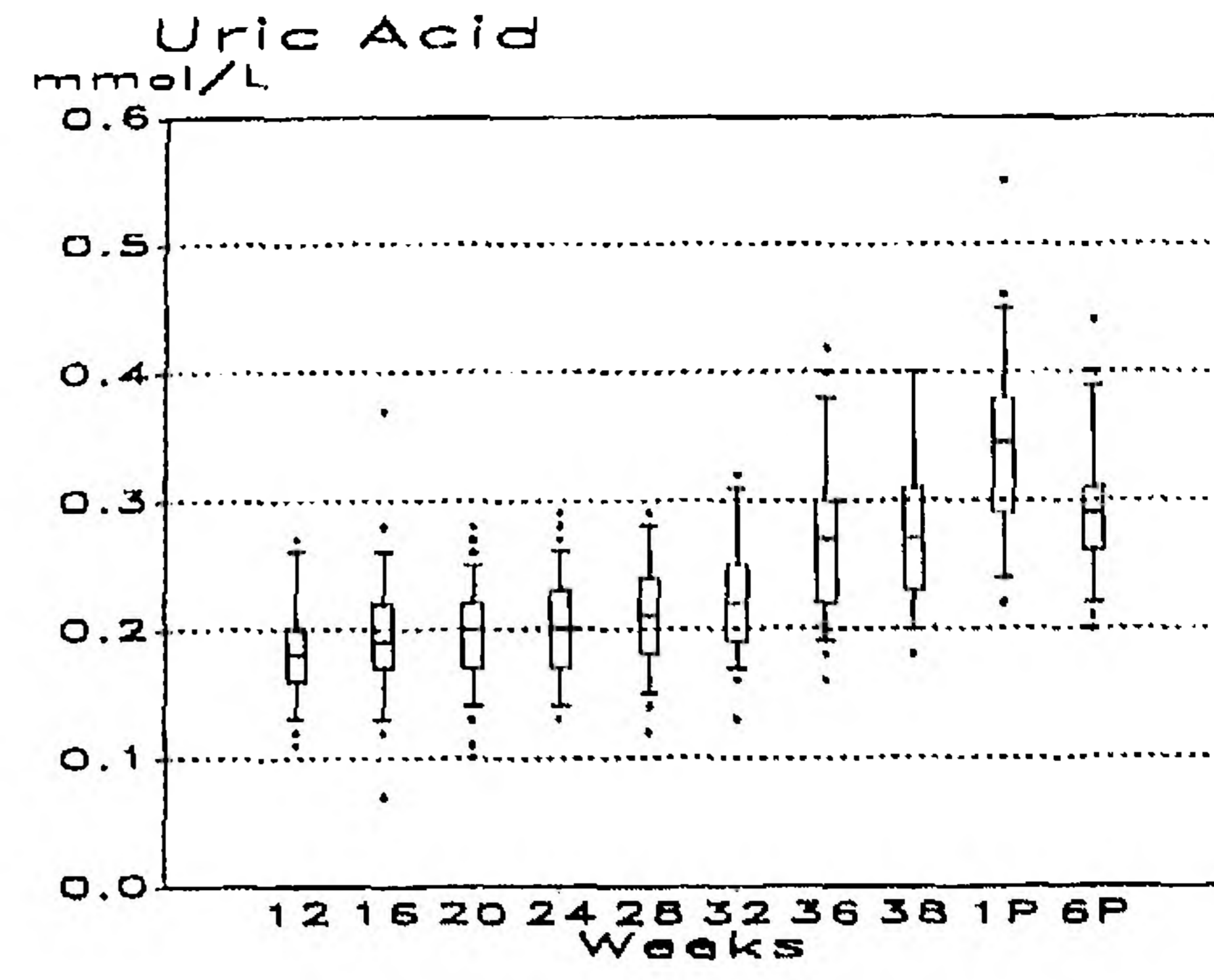
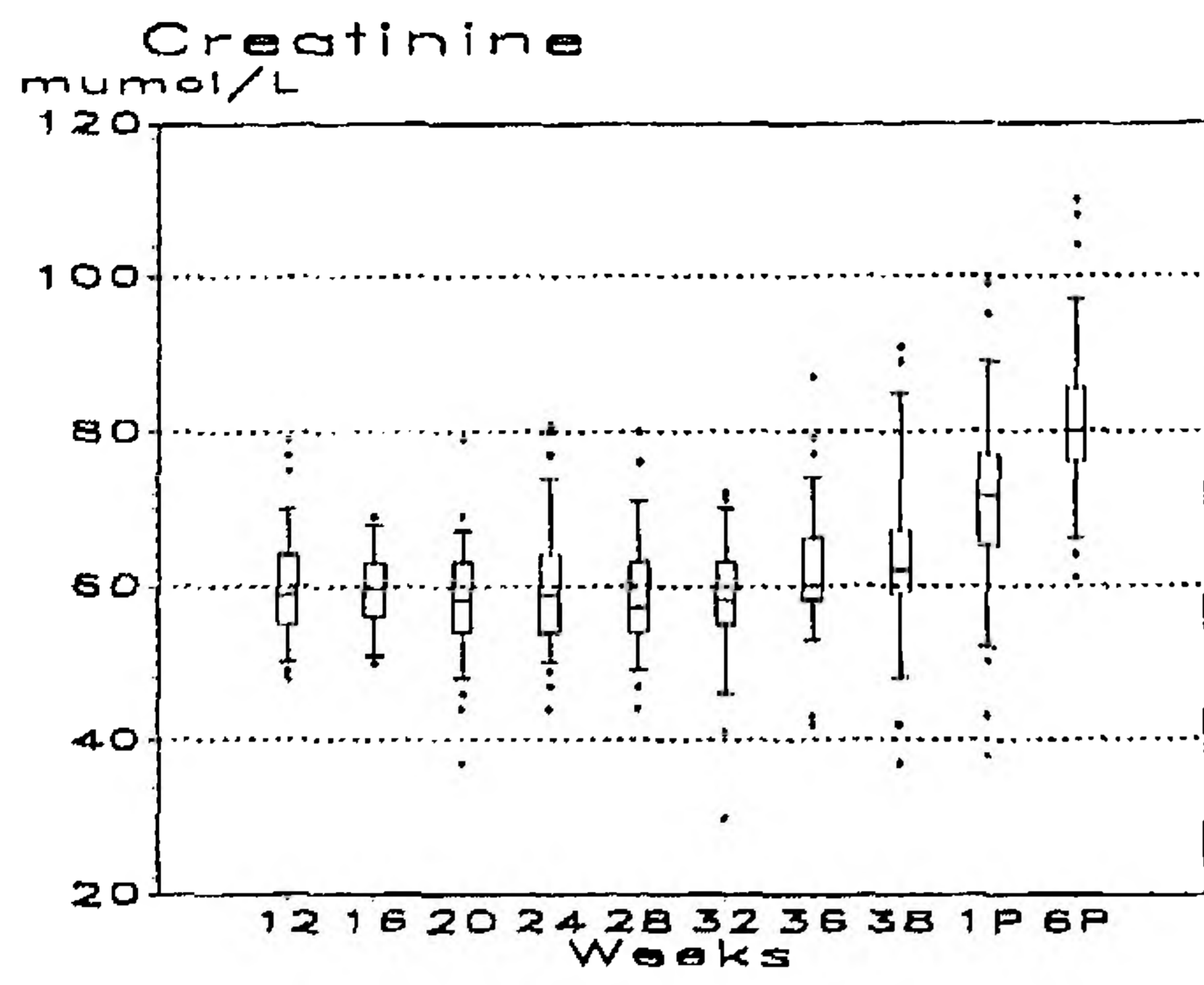
The highest median serum ferritin concentration was found in week 12 of pregnancy, and it declined afterwards by more than 50% during pregnancy to levels comparable with that at 6P. At 1P, the ferritin concentration was somewhat higher than at 6P (Table 4).

Serum concentrations of creatinine, urea, uric acid, electrolytes and proteins (Fig. 2)

Median serum creatinine and urea concentrations were significantly lower throughout pregnancy than at 6P: about 28 and 40% on average,

Fig. 1. Box and whisker plots of haematological parameters during pregnancy and puerperium. MCV = mean cell volume; MCH = mean cell haemoglobin; MCHC = mean cell haemoglobin concentration. The box displays the 75th and 25th centiles and the median, the whiskers indicate the 5th and 95th centiles. Values below the 5th centile and above the 95th centile are indicated as points outside the whiskers.





respectively. The median uric acid concentration in week 12 was 11 mmol/l (–38%) lower than at 6P. It increased gradually during pregnancy and in late gestation it was no longer different from the level at 6P.

Median serum sodium concentration was stable throughout pregnancy at about 138 mmol/l, but significantly lower than at 6P (142 mmol/l). The median serum chloride concentration was unchanged compared to the level post partum. The median serum potassium level during pregnancy was slightly, though significantly, lower than at 6P (–0.2 mmol/l). Total serum protein and albumen concentrations were markedly lower in the course of pregnancy than at 6P. The maximal difference of total protein was –8 g/l (–12%) in weeks 32 and 36, compared with week 6P. The lowest median serum albumen concentrations in weeks 32 and 36 were about 9 g/l (–21%) lower than those determined post partum.

Urinary excretion of electrolytes and creatinine (Fig. 3)

During pregnancy, urinary sodium excretion and sodium/creatinine ratios tended to be slightly higher compared with 6P, although differences reached statistical significance only at weeks 28 and 36. The median urinary chloride excretion and chloride/creatinine ratio were significantly elevated (approximately 20%) compared to 6P. Median urinary potassium excretion and potassium/creatinine ratios were about 15% higher during pregnancy than at 6P. Urinary excretion of creatinine during pregnancy did not differ from 6P. Throughout pregnancy, the median creatinine clearance was approximately 35% higher than at 6P.

Urine volume, osmolality of serum and urine, EFWC and FWC (Fig. 4)

U_{vol} during pregnancy was significantly higher (about 25%) than at 6P. S_{osmol} was significantly lower (about 9 mosmol/kg) during pregnancy. Similarly, the U_{osmol} was also slightly lower during

pregnancy than in the postpartum period. Statistical significance was reached from week 28 through week 38. Solute excretion levels were approximately 100 mosmol/24 h higher than those post partum, although there were no statistically significant differences. The FWC did not change very much during pregnancy. The EFWC was slightly higher during pregnancy, although only at week 32 was the difference statistically significant.

Serum concentrations of bilirubin, ASAT, ALAT, γ -GT, LDH and alkaline phosphatase (Table 4)

Concentrations of bilirubin, ASAT, ALAT and γ -GT in serum remained within the normal non-pregnant range throughout pregnancy and puerperium. The serum levels of LDH were slightly lower in early gestation than at 6P. However, LDH levels were markedly elevated at 1P (about 30%). In week 32, heat-stable alkaline phosphatase was about 6 times as high as at 6P and in week 12. Both heat-unstable and heat-stable alkaline phosphatase were significantly elevated at 1P.

4. Discussion

The present study describes the changes induced by pregnancy on various haematological and biochemical variables in a group of healthy nulliparous women who, after an uncomplicated pregnancy, delivered an healthy baby with a normal birth weight.

Haematological data

Our findings on Hb, Ht and erythrocyte count confirm those of other serial studies in pregnant women receiving iron supplements [13,14]. The changes in Hb and Ht can be explained by the well-known changes in plasma volume and red cell mass in pregnancy. The plasma volume increases between the 6th and the 30th week of pregnancy by about 1250 ml [15]. The increase in

Table 4
Serum concentrations of liver enzymes and ferritin

	Week 12	Week 32	1P	6P
Ferritin ($\mu\text{g/l}$)	40 * (6-130)	13 (3-95)	24 ** (3-94)	17 (3-97)
Total Bilirubin (IU/l)	4 * (1-12)	4 * (2-9)	4 * (2-10)	5 * (2-70)
ASAT (IU/l)	9 * (4-18)	9 ** (5-21)	11 (5-103)	10 (6-27)
ALAT (IU/l)	9 * (4-30)	8 * (2-22)	12 (5-115)	12 (3-54)
γ -GT (IU/l)	7 (2-18)	6 (3-20)	9 * (5-79)	7 (4-23)
LDH (IU/l)	186 * (138-328)	194 (127-272)	259 * (165-398)	192 (147-279)
Alkaline phosphatase (IU/l)				
Total	42 * (17-88)	82 * (46-165)	97 * (48-249)	63 (20-117)
Unstable	37 * (4-74)	48 * (20-96)	70 * (6-183)	57 (14-104)
Stable	5 (1-51)	32 * (9-80)	33 * (7-78)	5 (1-69)

Values are medians (min-max). Statistical significance (Wilcoxon signed rank) in comparison with 6P: * $p < 0.01$; ** $p < 0.05$.

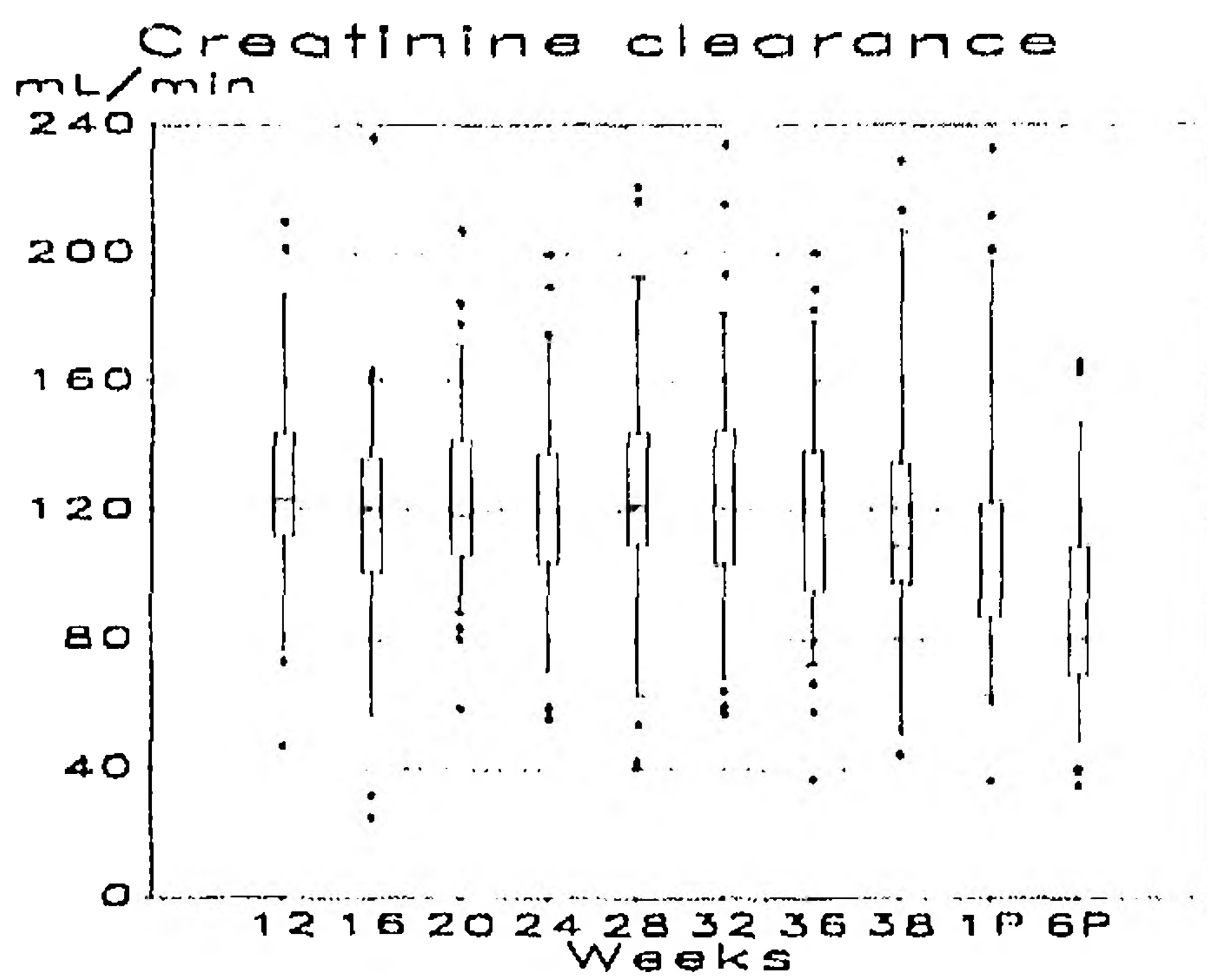
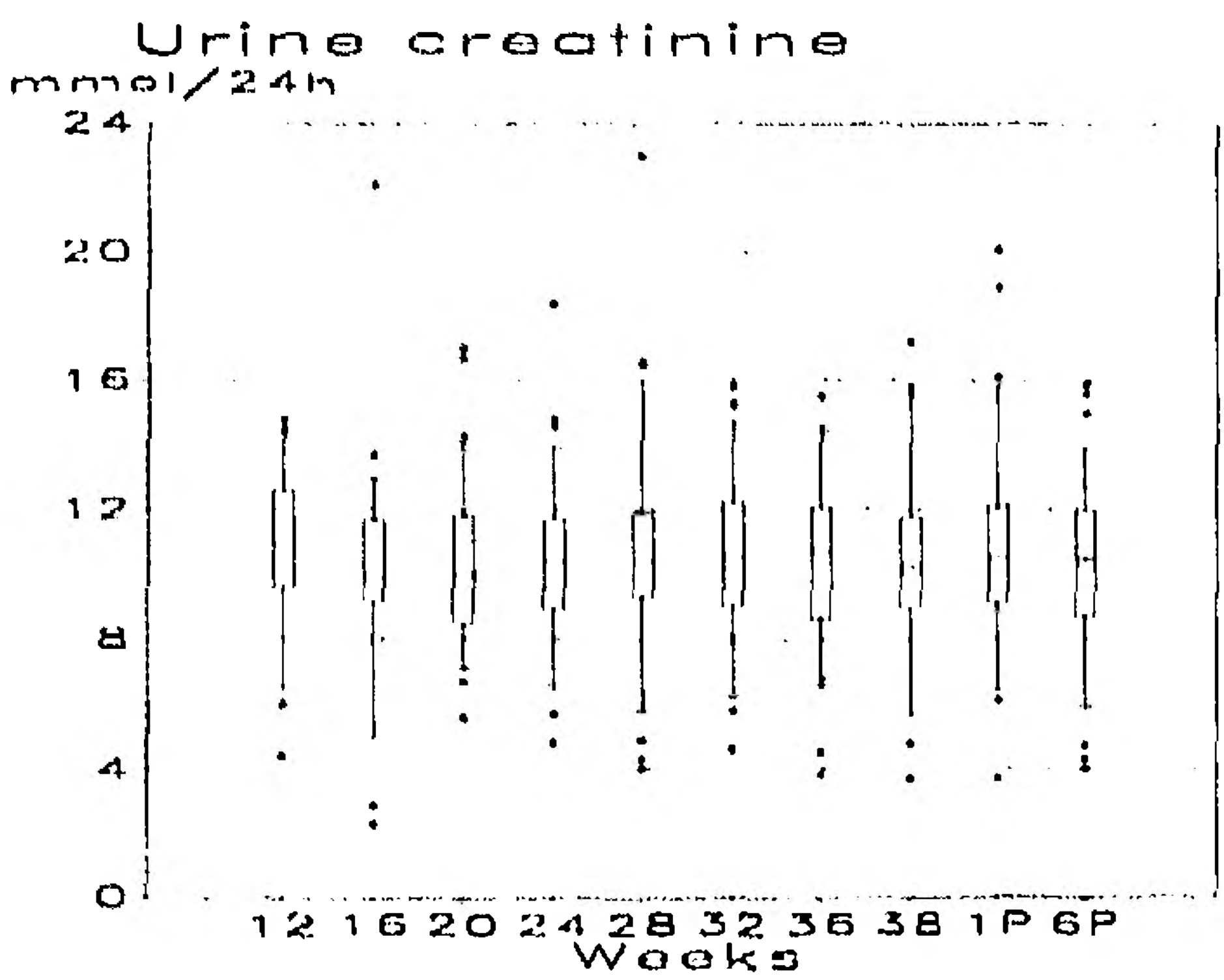
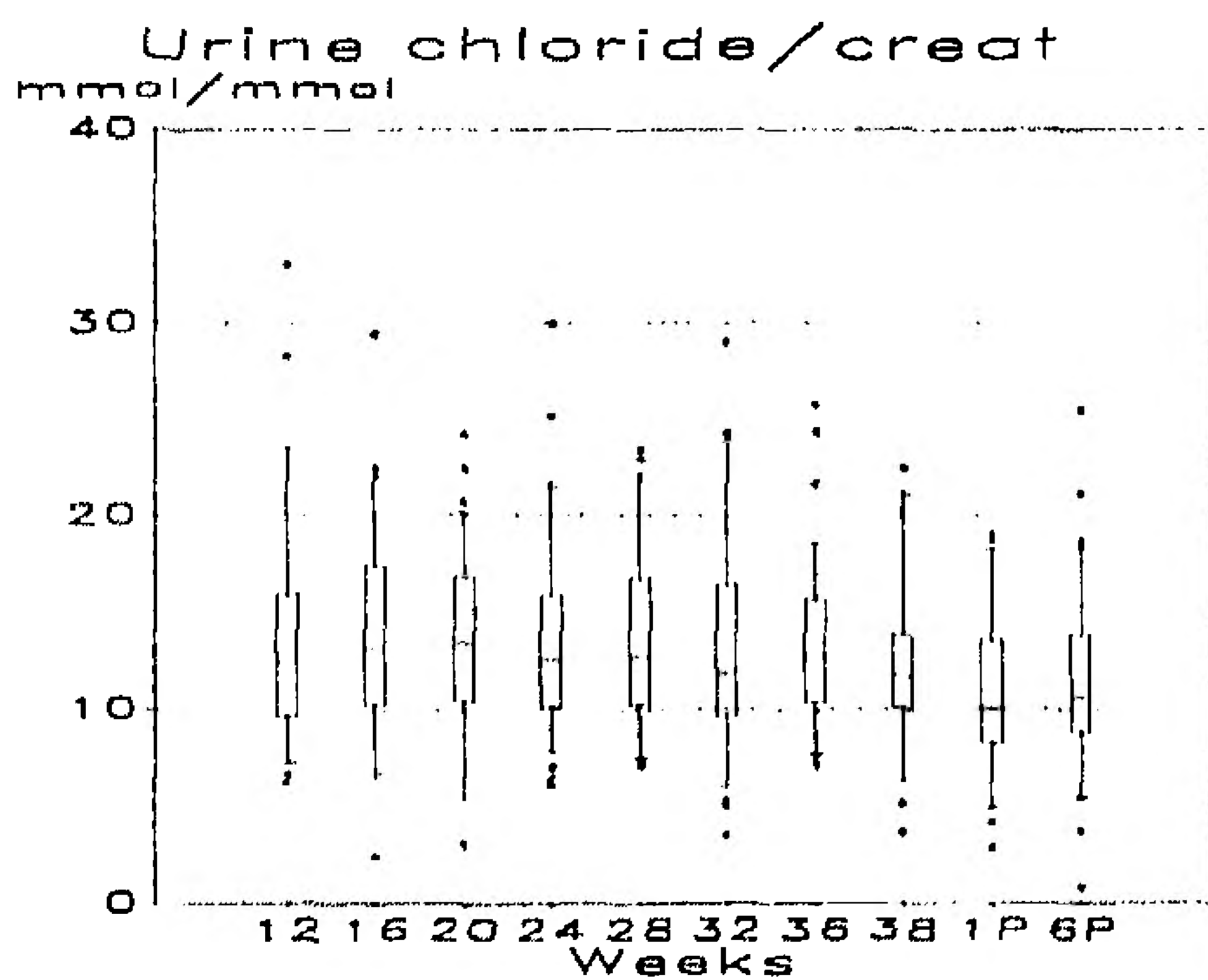
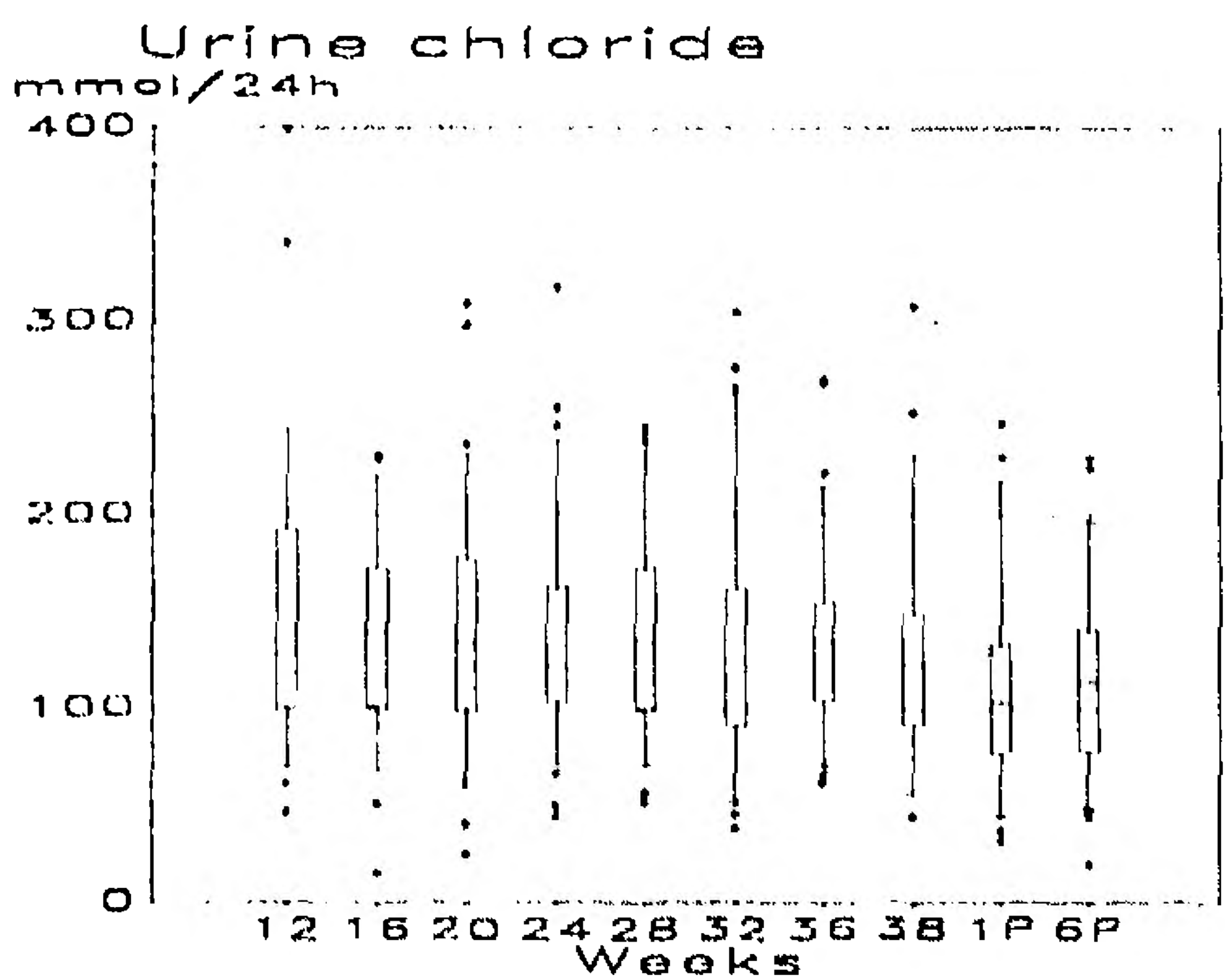
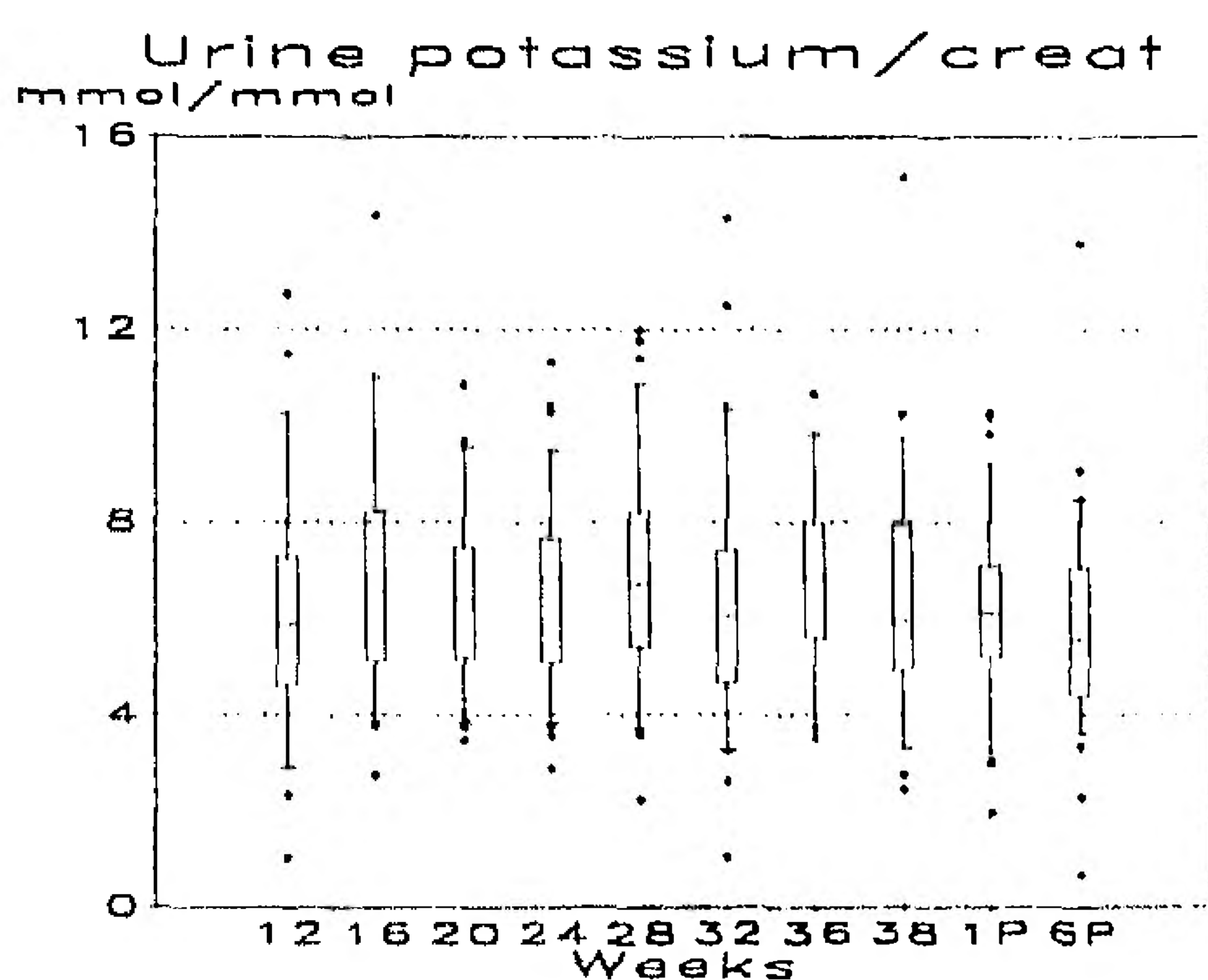
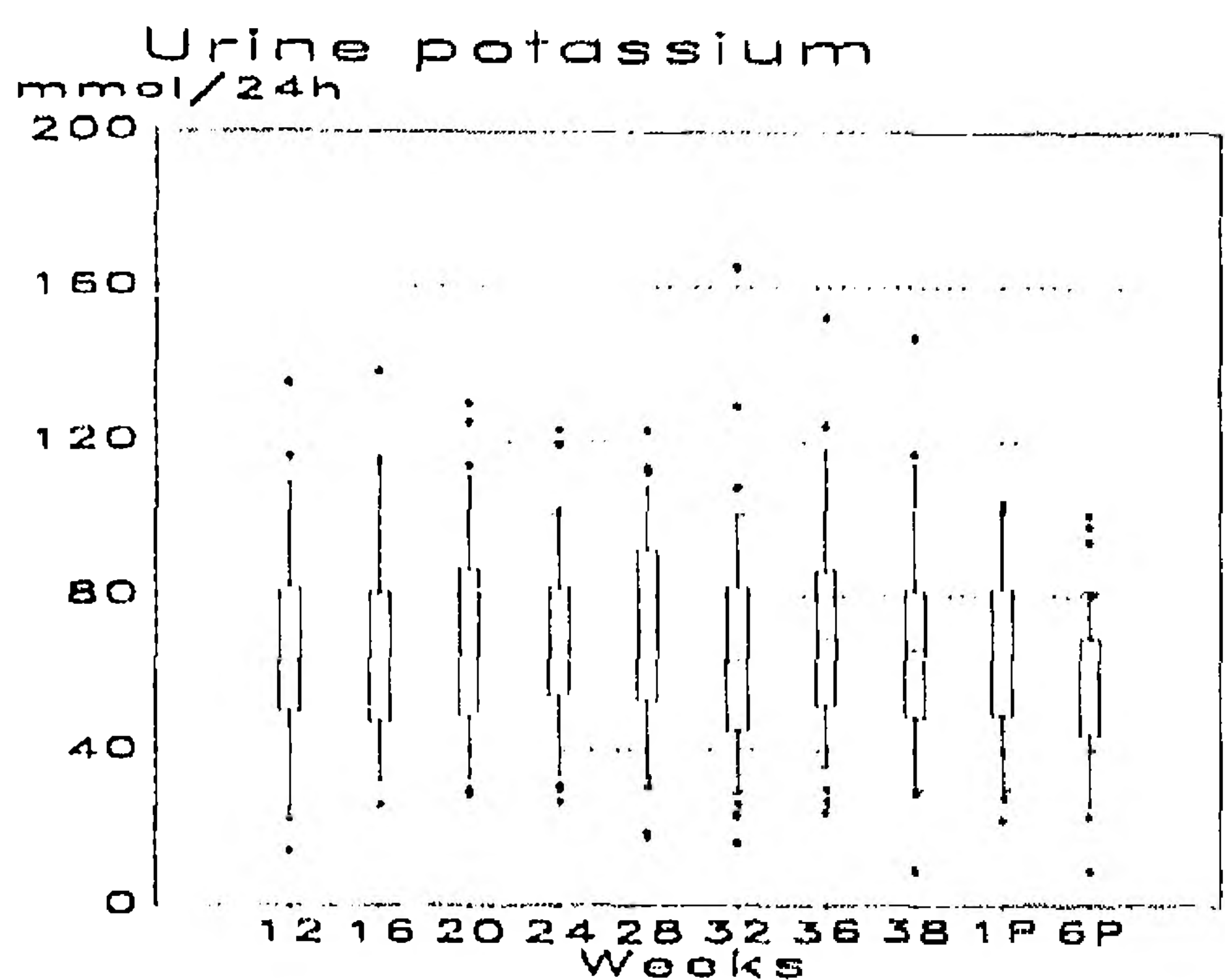
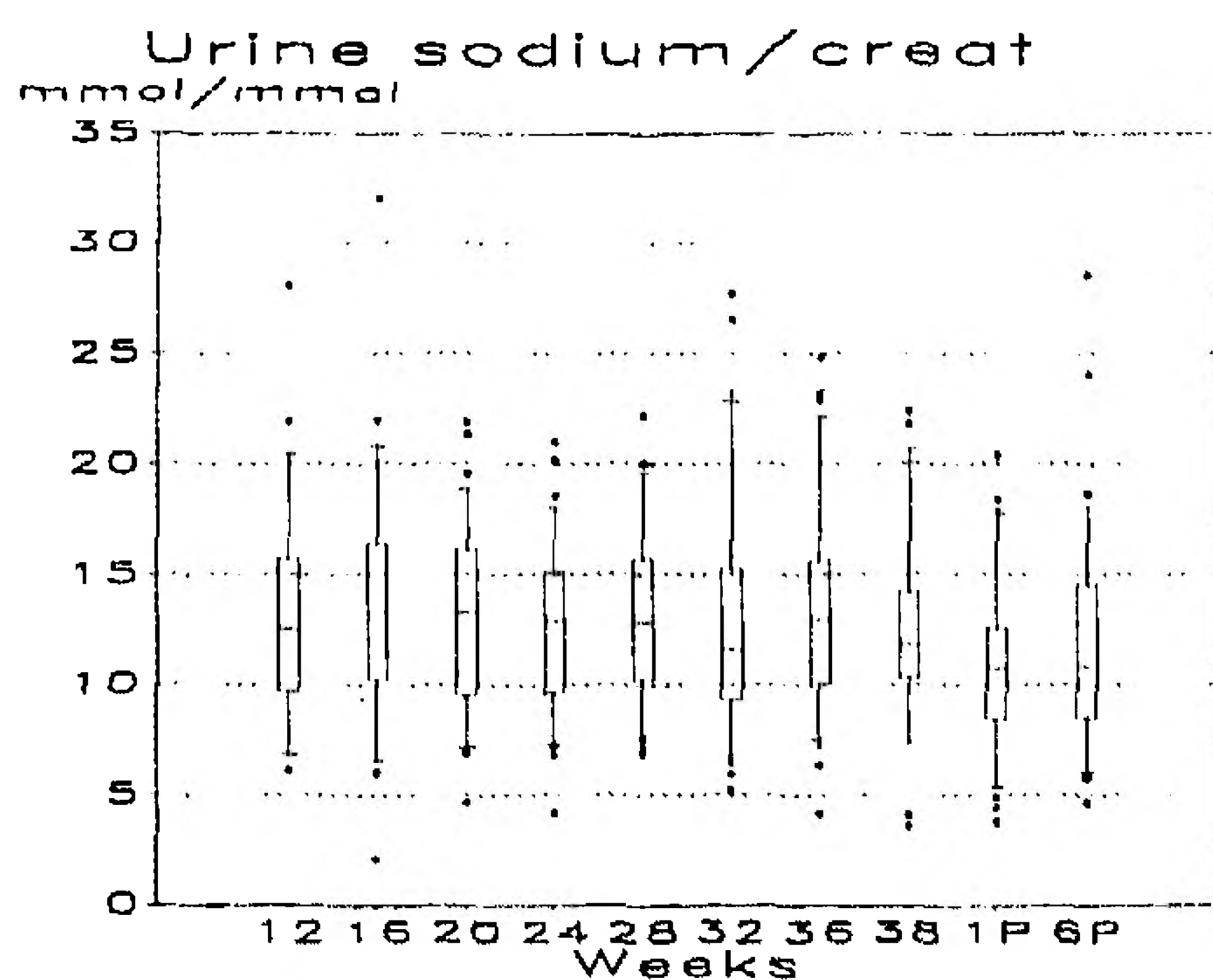
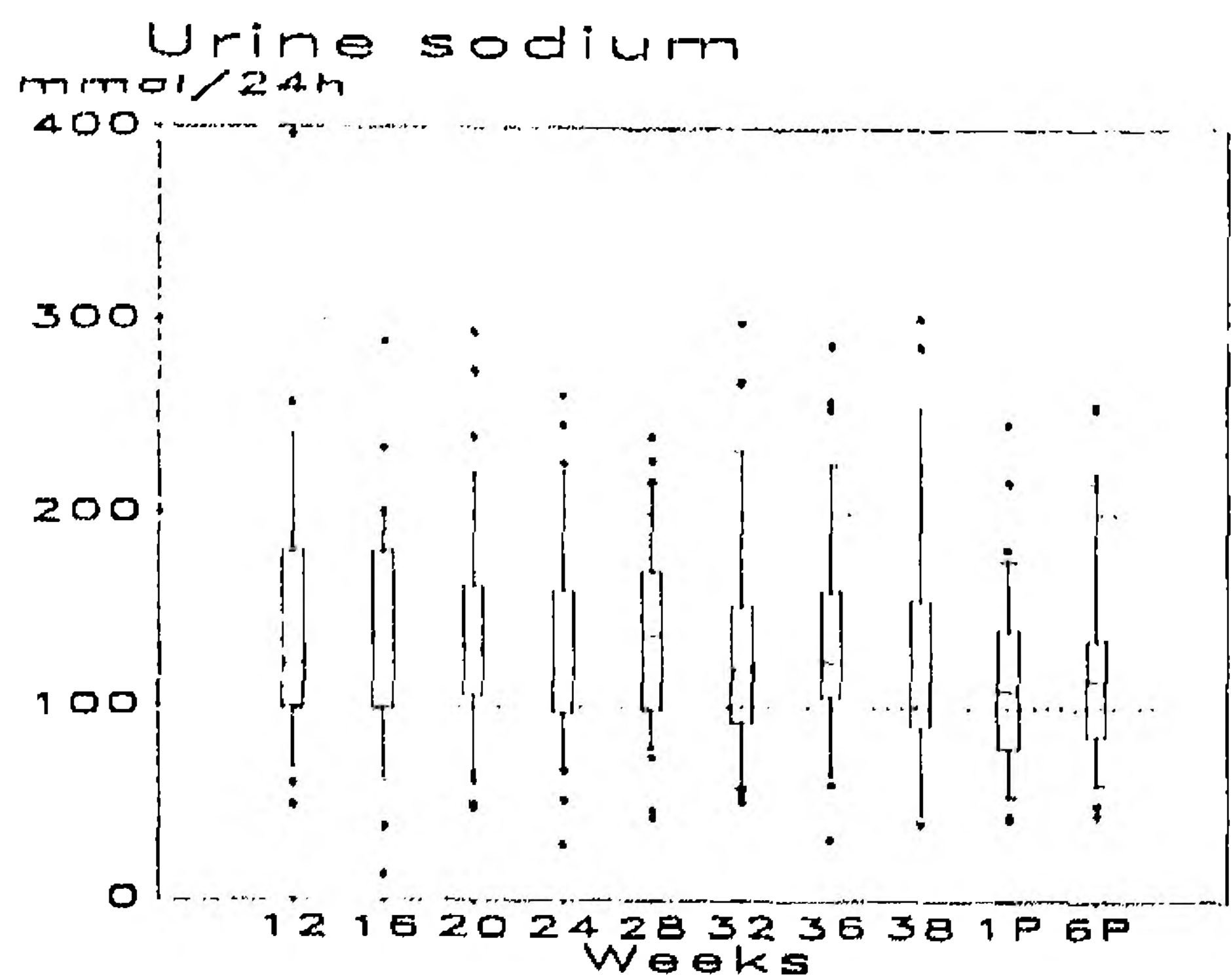
red cell mass between weeks 12 and 36 has been found to be approximately 280 ml if no supplements are used and around 450 ml if iron and folate are supplemented [16]. The discrepancy between rate of increase in plasma volume and that in red cell mass leads to a physiological decrease in Hb, Ht and erythrocyte count in mid-pregnancy. In a study without iron supplementation, serum ferritin concentrations at 6 months after delivery were still significantly lower than in the early stage of pregnancy, suggesting that pregnancy without iron supplementation leads to depletion of the iron stores [17].

The platelet count was stable throughout pregnancy, which confirms other studies [18-21], although a small decrease in late pregnancy has been reported [22]. On the 7th postpartum day, the platelet count was 60% above the late gesta-

tional level. Others have reported similar increases in the first week post partum [23-25]. The temporary increase in the platelet count after delivery must be considered as a compensatory increase in platelet production after a period of platelet consumption during separation and delivery of the placenta. The peak platelet count lasts at least two weeks because the life span of platelets is about 8-11 days. [26]. The higher platelet count may contribute to the increased risk of thromboembolic complications in the puerperium.

Probably as a result of increased production in the liver, serum fibrinogen was higher during pregnancy than after delivery, which confirms other studies [23,27]. Both serum total protein (-12%) and serum albumin (-21%) concentrations decreased considerably during pregnancy.

Fig. 3. Box and whisker plots of urine sodium excretion, urine sodium/creatinine ratio, urine potassium excretion, urine potassium/creatinine ratio, urine chloride excretion, urine chloride/creatinine ratio, urine creatinine excretion and creatinine clearance during pregnancy and puerperium. Urine sodium/creat = Urine sodium/creatinine ratio; Urine potassium/creat = Urine potassium/creatinine ratio; Urine chloride/creat = Urine chloride/creatinine ratio. Plot symbols are explained in Fig. 1.



The decrease in the serum albumin explains the major portion of the decrease in total protein [28].

Serum concentrations of electrolytes

The drop in serum sodium concentration of 4 mmol/l that was observed is in good agreement with the data of other longitudinal studies [29–31].

Serum potassium levels decreased slightly during pregnancy. The decrease in serum potassium has been reported previously [29], although others did not observe a change during pregnancy [31]. Serum chloride concentration was unaltered in pregnancy. Newman [29] observed a minor decrease in the serum chloride concentration during pregnancy.

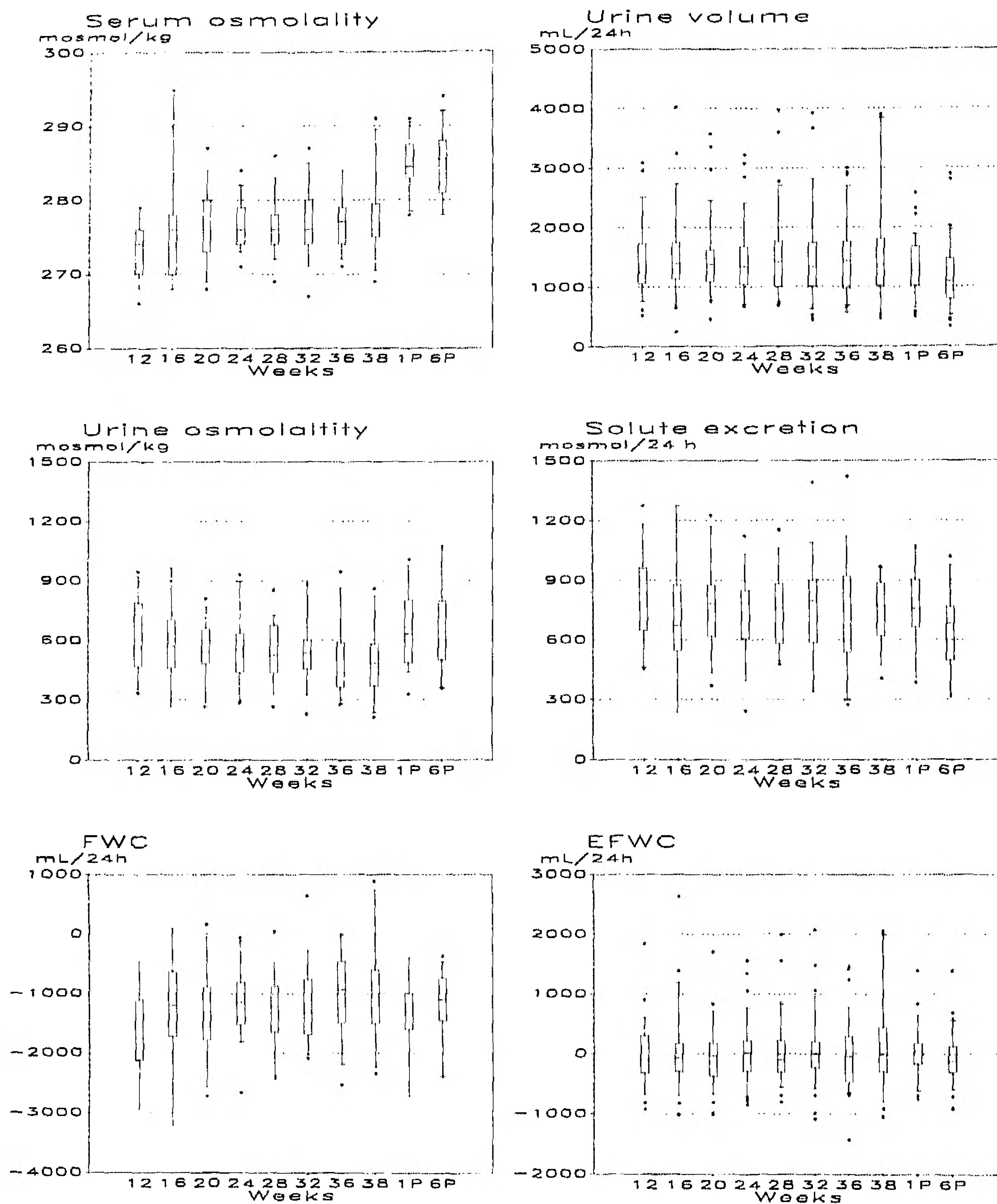


Fig. 4. Box and whisker plots of serum osmolality, urine volume, urine osmolality, solute excretion, free-water clearance (FWC) and electrolyte-free water clearance (EFWC) during pregnancy and puerperium. Plot symbols are explained in Fig. 1.

Urinary excretion of electrolytes

The cumulative requirements during pregnancy of sodium and of potassium were estimated to be 987 and 320 mEq, respectively [32]. This implies a daily retention of about 3–4 mmol of sodium and of 1–2 mmol of potassium. The urinary excretion of sodium tended to increase during pregnancy in our study. Potassium excretion during pregnancy was moderately enhanced. Brown et al. [33] found no significant change in pregnancy compared to post partum values. One would expect that the high mineralocorticoid concentrations during normal pregnancy would cause considerable urinary potassium loss, but high progesterone levels seem to attenuate the kaliuretic effects of these mineralocorticoids [34].

Creatinine, urea and uric acid

The changes in creatinine clearance and the serum concentrations of creatinine, urea and uric acid confirm the results of other studies [35–40]. The uric acid clearance decreases in late gestation without a decrease in inulin clearance. The renal handling of uric acid appears to change in the course of pregnancy, resulting in increased tubular re-absorption in late gestation [39].

Urine volume, osmolality of serum and urine, EFWC and FWC

U_{vol} was 25% higher during pregnancy than at 6P, EFWC tended to be higher, S_{osmol} and U_{osmol} decreased considerably, whereas FWC remained unaltered. The amount of water excreted in the urine consists of two fractions: a fraction necessary to excrete the solutes in a solution that is iso-osmotic to plasma and a fraction of free-water (FWC). If the urine is hyperosmotic to plasma, then the FWC is negative. U_{vol} normally mirrors the oral fluid intake, implying that fluid intake is increased during pregnancy. Our data suggest that the increment in the solutes that have to be excreted explains the major part of the enhanced urine volume. Although the excretion of solutes was not significantly changed during pregnancy, the median values were at most of the time-points about 100 mosmol/24 h higher than those in the non-pregnant situation. If 100 mosmol have to be

excreted in an iso-osmotic solution to plasma, i.e. about 275 mosmol/kg, then 0.364 kg of water is required. This corresponds well with the observed increment in urine volume in pregnancy. Increased urine volumes in pregnancy have been reported previously [41], while others found no significant differences [42]. Of interest in the regulation of U_{vol} is the osmotic threshold for arginine-vasopressin (AVP) release. The osmotic threshold for thirst is about 5 mosmol/kg higher than that for AVP release. Both thresholds decrease by about 10 mosmol/kg during human pregnancy [43]. The decrease of the two osmotic thresholds and the resulting decrease of the P_{osmol} has been attributed to human chorionic gonadotrophin (hCG), because treatment with hCG in non-pregnant women also results in a decline of the two osmotic thresholds and P_{osmol} with approximately 5 mosmol/kg [44]. Obviously some caution must be taken while interpreting the results on urinary parameters, due to possible incomplete collection of 24-h urine samples. However, if present, these inadequacies appear to be comparable during and after pregnancy as mean urinary creatinine excretions were in the same range in all periods studied. This means that trends are still detectable.

Serum concentrations of bilirubin, ASAT, ALAT, γ -GT, LDH and alkaline phosphatase

The increase in total, heat-stable and heat-unstable alkaline phosphatase is well known. Both placental alkaline phosphatase (heat-stable) and bone alkaline phosphatase (heat-unstable) increase whereas liver alkaline phosphatase (heat-unstable) remains unaltered. Six weeks after delivery, placental alkaline phosphatase returns below the detection limit, but the bone isoenzyme is still above the baseline value [45]. The LDH concentration in serum either remains unaltered or increases only to a small extent during normal pregnancy [46]. The observed enhancement of serum LDH at 1 week after delivery could originate from the uterine muscles, due to the involution of the uterus, and from damaged erythrocytes involved in the haemostatic process in the placental bed.

5. Conclusions

The reference values of most investigated routine laboratory parameters change during pregnancy and the puerperium. Physicians treating pregnant women must be aware of the physiological changes that occur during pregnancy to avoid misinterpretation of results of laboratory investigation, leading to erroneous diagnoses and hence to incorrect treatment or unjustified abstinence from treatment.

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