

# Plasma 17-hydroxyprogesterone in newborn infants with congenital adrenal hyperplasia and in infants with normal adrenal function

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**Atherden, S. M., Edmunds, A. T., and Grant, D. B. (1974).** *Archives of Disease in Childhood*, 49, 192. **Plasma 17-hydroxyprogesterone in newborn infants with congenital adrenal hyperplasia and in infants with normal adrenal function.** Plasma 17-hydroxyprogesterone (17-OHP) was estimated in 9 infants aged 6 to 12 days with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Raised plasma 17-OHP values, ranging from 3.4 to 25.0  $\mu\text{g}/100$  ml were found. 50 infants aged 10 hours to 15 days with normal adrenal function were also studied. One infant with galactosaemia had 17-OHP levels of 1.8 and 2.4  $\mu\text{g}/100$  ml, and a further 3 infants aged 15 hours to 3 days had 17-OHP levels between 1.1 and 2.1  $\mu\text{g}/100$  ml. In the remaining infants, plasma 17-OHP was less than 1.0  $\mu\text{g}/100$  ml. It therefore appears that estimation of plasma 17-OHP provides a useful method for confirming the diagnosis of CAH during the newborn period.

Congenital adrenal hyperplasia (CAH) is due, in the majority of cases, to a deficiency of 21-hydroxylase, the enzyme required for the hydroxylation of 17-hydroxyprogesterone (17-OHP) in the biosynthesis of cortisol. This results in a conspicuous rise of the plasma 17-OHP concentration (Strott, Yoshimi, and Lipsett, 1969).

We have described a simple method for estimating plasma 17-OHP (Barnes and Atherden, 1972), and the present paper gives results obtained with this method in infants with normal adrenal function and in newborn infants with CAH or suspected CAH.

## Patients and methods

### Patients.

**Infants with CAH.** Specimens were obtained from 3 male and 6 female infants aged 6 to 12 days with CAH. The diagnosis was confirmed in these patients by analysis of urinary steroids. 6 had the salt-losing form of the disorder.

**Infants with suspected CAH.** Plasma samples were obtained from 9 infants aged 18 hours to 14 days in whom CAH was suspected because of persistent vomiting, abnormal external genitalia, or a family history of the

disorder. In all these patients, the diagnosis of CAH was excluded by the subsequent clinical and laboratory findings.

**Infants with normal adrenal function.** 49 specimens were collected from 41 infants without evidence of adrenal disease at the same time as blood was taken for investigation of conditions such as jaundice, hypoglycaemia, or suspected sepsis. 23 infants were male and 18 were female, ages ranging from 10 hours to 15 days.

**Methods.** Heparinized blood samples were obtained by heel prick or venepuncture between 9.00 and 12.00 hours. Plasma samples were stored frozen until used.

Details of the method used to estimate plasma 17-OHP have been published elsewhere (Barnes and Atherden, 1972).

## Results

Plasma 17-OHP results for the three groups of patients are shown in the Fig.

**Infants with CAH.** Plasma 17-OHP levels were raised in all the infants with CAH, ranging from 3.4 to 25.0  $\mu\text{g}/100$  ml.

Two samples were obtained from 3 patients. In 1 the plasma 17-OHP rose from 6.0  $\mu\text{g}/100$  ml on

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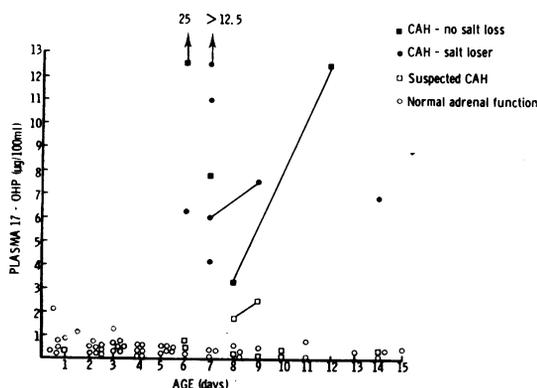


FIG.—Plasma 17-hydroxyprogesterone (17-OHP) levels in 9 infants with congenital adrenal hyperplasia (CAH), 9 infants with suspected but unconfirmed CAH, and 40 infants with normal adrenal function.

day 7 to 7.5  $\mu\text{g}$  on day 9, and in another from 3.4  $\mu\text{g}/100$  ml on day 8 to 12.5  $\mu\text{g}$  on day 12. In one infant aged 7 days the morning 17-OHP value was greater than 12.5  $\mu\text{g}/100$  ml and the midnight value was 10.0  $\mu\text{g}$ .

**Infants with suspected CAH.** Plasma 17-OHP levels of 1.8  $\mu\text{g}/100$  ml (day 8) and 2.4  $\mu\text{g}/100$  ml (day 9) were found in 1 infant with galactosaemia who was extremely ill with persistent vomiting, dehydration, and jaundice. The urinary 11-oxygenation index (Clayton, Edwards, and Makin, 1971) was abnormally raised in this patient, but normal adrenal glands were found *post mortem*. The liver showed gross fatty changes.

In the remaining 8 patients plasma 17-OHP levels were less than 1.0  $\mu\text{g}/100$  ml.

**Infants with normal adrenal function.** In 45 samples from 37 infants, plasma 17-OHP values below 1.0  $\mu\text{g}/100$  ml were obtained. In one infant aged 15 hours plasma 17-OHP was 2.1  $\mu\text{g}/100$  ml and in 2 further infants aged 2 and 3 days the levels were 1.1  $\mu\text{g}$  and 1.3  $\mu\text{g}$ , respectively.

A heavily haemolysed sample from an infant aged 6 days gave a 17-OHP value of 4.2  $\mu\text{g}/100$  ml (not shown in the Fig.). The extract from this sample was discoloured and this almost certainly accounted for the abnormal result. 17-OHP could not be detected in a further sample from this infant.

### Discussion

Tests for CAH which are based on analysis of urinary steroids may give misleading results during the newborn period. In normal infants urinary

17-oxosteroid excretion is usually slightly raised during the first few days of life. Conversely, in infants with 21-hydroxylase deficiency, pregnane-triol may not be found in the urine during this period (Shackleton, Mitchell, and Farquhar, 1972). In addition, false-positive or false-negative results may be obtained for the urine 11-oxygenation index (Clayton *et al.*, 1971).

The findings reported by Jenner, Grumbach, and Kaplan (1970) and by Franks (1972), together with the results described in this paper, indicate that estimation of plasma 17-OHP may provide a more reliable method for confirming the diagnosis of CAH during the neonatal period. Jenner *et al.* (1970) found a plasma 17-OHP value of 5.7  $\mu\text{g}/100$  ml in a 4-day-old infant with CAH and Franks (1972) reported an average 17-OHP level of 44.8  $\mu\text{g}/100$  ml in 4 infants with CAH who were less than a month old. In the present study, conspicuously raised 17-OHP levels were found in 9 infants with CAH aged 6 to 14 days, and it therefore appears that a high proportion of infants with 21-hydroxylase deficiency have raised plasma 17-OHP levels by the end of the first week of life. As our youngest patients were 6 days old, the results do not permit any conclusions as to how soon after delivery abnormally high 17-OHP levels can be detected. It is still not known whether patients with a very mild form of CAH have raised 17-OHP levels soon after birth, but it seems unlikely that false-negative results will be common in patients with the salt-losing form of the disorder.

In older children with defective 21-hydroxylation there is a marked circadian variation in plasma 17-OHP, and relatively low values may be found in the late evening (Atherden, Barnes, and Grant, 1972). In the present study all but one of the specimens were obtained between 9.00 and 12.00 hours and we have not systematically investigated the possibility that plasma 17-OHP levels may vary at different times of the day in newborn infants. However, as the adult circadian pattern of corticotrophin secretion is probably absent in young children (Franks, 1967), it seems that the time when samples are obtained is unlikely to be important during the neonatal period. This conclusion is supported by our findings in one infant who showed a conspicuous rise of plasma 17-OHP in a sample collected at midnight.

While the method used in this study is relatively simple, it is not specific for 17-OHP and any progesterone which is present will also be extracted and estimated. As the plasma progesterone concentration in CAH is only about 3 to 13% of that of 17-OHP (Strott *et al.*, 1969; Simopoulos *et al.*

1971), and as progesterone shows less than half the competition for the assay binding protein when compared with 17-OHP (Barnes and Atherden, 1972), errors caused by this lack of specificity are likely to be small in patients with CAH. However, it was important to establish that the relatively high plasma progesterone levels found at birth in normal infants (Conly *et al.*, 1968) did not invalidate results obtained during the early neonatal period. The above results indicate that the method rarely gives 17-OHP values above 1  $\mu\text{g}/100\text{ ml}$  after the first day of life in normal infants. However, the findings in an infant with galactosaemia suggest that moderately high 17-OHP values may be obtained occasionally in extremely ill infants who do not have CAH. It is of interest that the 11-oxygenation index was also raised in this case.

Many of the samples used in this study were icteric or slightly haemolysed. Though such samples are suitable for estimation of plasma 17-OHP, results obtained with heavily haemolysed specimens should be viewed with suspicion as discoloration of the plasma extract is likely to invalidate the method. High 17-OHP values obtained under these conditions should be confirmed using a further unhaemolysed sample.

We thank the paediatricians who referred patients to us with CAH or suspected CAH.

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