liver, with the exception of factor VIII which is produced by endothelium. In the presence of severe liver disease there is a failure to synthesise the clotting factors, leading to progressive failure of coagulation, with low concentrations of all the clotting factors except factor VIII. These findings were present in our patients and suggest that defective hepatic synthesis, due to the liver failure of tyrosinaemia, contributed largely to the clotting defect.

Reptilase clots fibrinogen by splitting off fibrinopeptide A, in contrast to thrombin which splits off fibrinopeptides A and B. With normal plasma, the thrombin and Reptilase times are similar. Heparin prolongs the thrombin time but leaves the Reptilase time only slightly affected. When the fibrinogen molecule is abnormal, however, that is in dysfibrinogenaemia, the clotting time with Reptilase is proportionately far longer than the clotting time with thrombin.[6] The Reptilase time has been used as a screening test for abnormal fibrinogen in liver disease.[7 8] All three babies showed a Reptilase time much longer than the thrombin time, and on this evidence had dysfibrinogenaemia. They also had anaemia, thrombocytopenia, and hypofibrinogenaemia. Blood films showed red cell fragmentation and in case 1 there was an increase of fibrinogen degradation products. These findings are evidence that a consumption coagulopathy was also contributing to coagulation failure.

Case 3 developed septicaemia which is a recognised cause of disseminated intravascular coagulation and defibrination in babies[4] but we did not observe septicaemia in cases 1 and 2. These findings cannot, therefore, all be attributed to infection. It seems reasonable to conclude that the haemorrhagic defect in the acute form of hereditary tyrosinaemia is the result of hepatic disease. The indicated treatment would seem to be replacement with fresh plasma, blood, platelets, and fibrinogen. In case 3, however, this treatment failed to reverse the defect, probably because of persisting defibrination to which the septicaemia may have contributed. It seems unlikely that the coagulation defect will be treatable without curing the primary hepatic defect.

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Correspondence to Dr D I K Evans, The Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA.

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Postnatal breast development of preterm infants

An index of gonadal function

J McKIERNAN

Paediatric Department, Regional Hospital, Cork, Ireland

SUMMARY Development of breast nodules after birth was examined in 17 preterm infants; nodules developed regularly in girls but not boys. It is concluded that the pituitary-gonadal axis of preterm infants is active in the months after birth and that in preterm infants there is a definite phase of breast growth in early postnatal life.

In recent years there has been much interest in the development of gonadal function in early life. In boys there is evidence for a surge of testicular androgen secretion after birth, with a peak at about 8 weeks of age.[1] In those born preterm this postnatal testosterone secretion may be even greater.[2] It is not known what contribution, if any, the fetal ovary makes to oestrogen production during pregnancy but during the first postnatal weeks oestrogen

concentrations fall rapidly.[3] Thereafter concentrations of oestrogen rise again in both sexes—in boys there is a peak at about 2 months after which values fall, reaching prepubertal concentrations by 6 months of age. In girls, oestrogen concentrations are higher than in boys and do not fall to prepubertal values until the age of about 1 year. There is little information on oestrogen secretion in preterm infants during this time, partly because of the relatively large volumes of blood needed for assay. It has recently been shown that in mature infants of both sexes there is a normal phase of breast growth after birth which is more prolonged in girls.[4] Most preterm infants of 34 weeks' gestation or less, unlike term babies, have little or no palpable breast tissue at birth. The growth of breast tissues may be regarded as a sensitive 'bioassay' for oestrogen. It was decided, therefore, to study the development of breast tissue after birth in preterm infants as an index of oestrogen production.

Subjects and methods

Seventeen preterm infants who did not have any palpable breast tissue at birth were selected for study and were subsequently examined at intervals over the first year of life as they attended for regular follow up evaluation. Details of birthweight and gestation are given in the Table. Breast development was assessed by palpation of the breast area. If no breast tissue was palpable on either side, breast development was stage 0; if a small nodule less than 0·5 cm was felt, stage 1 was assigned, and if a definite nodule greater than 0·5 cm was present stage 2 was assigned.

Results

Definite nodules of breast tissue developed in 10 of the 11 girls during the first months of life and persisted for varying periods (Figure). Breast development did not occur in one girl, and here the duration of follow up to date may have been too short. Only two of the boys developed breast nodules and in four no breast development was seen over the first 5 to 10 months of life. Postnatal breast growth in the infants studied did not seem to be affected by illnesses at birth or problems later in infancy.

Table *Clinical details of the infants*

	Gestation (weeks)		*Birthweight (g)*	
	Mean	*Range*	*Mean*	*Range*
Boys (n=6)	31	28–34	1·3	1·1–1·6
Girls (n=11)	30	28–35	1·3	0·9–2·0

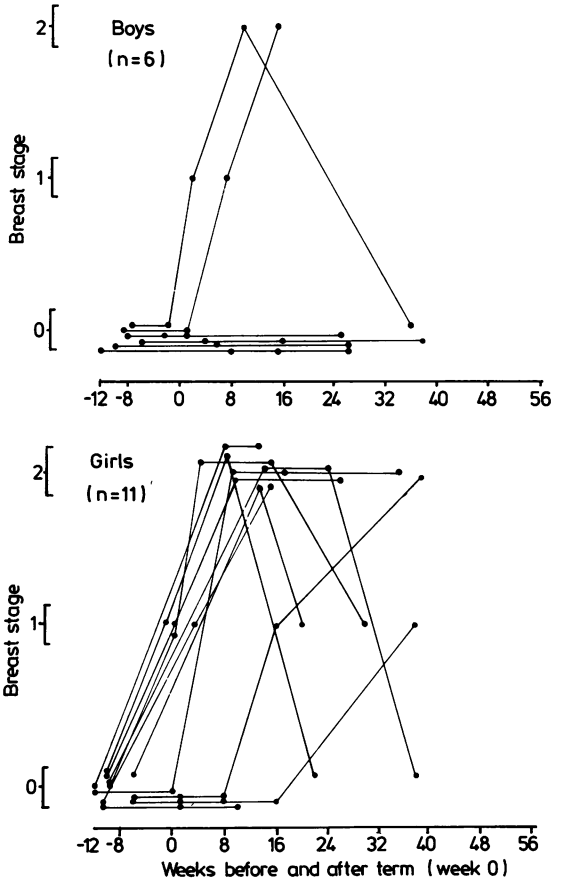

Figure *Breast development in male and female preterm infants in relation to postnatal age, expressed as weeks before and after term.*

Discussion

Although the numbers, especially of boys, are small, this study shows that there is a definite phase of breast development after birth in many preterm infants. This cannot be due to the effects of pregnancy or maternal oestrogens which are rapidly cleared from the circulation. It is interesting that there was a sex difference in this phase of postnatal breast growth as in mature newborn infants there is no sex difference in breast development at birth or during the first few months of life, and such a difference is not seen until the age of 6 months.[4] This may be because postnatal breast engorgement,

which is quite noticeable in many term infants, obscures real differences in the size of the underlying breast nodule, while in preterm infants this postnatal breast engorgement does not occur.

It is known that circulating oestradiol concentrations are relatively high in normal infancy, and especially in girls.[3] The development of breast tissue by preterm girls suggests that not only is there active oestrogen secretion by the ovary but that this is biologically active. Breast development seen in the boys might reflect activity of oestrogen secreted by the testis, or could be due to peripheral conversion from androgen.

Growth hormone[5] and prolactin[6] concentrations are higher in preterm than term infants after birth and raised follicle stimulating hormone and luteinising hormone concentrations after the first week of life have been reported recently in preterm girls.[2] It is not possible to know from the present study if there is enhanced pituitary-gonadal activity in girls who are born preterm, but certainly there is no indication of impaired gonadal function. Breast development was seen in two boys only; this may reflect stimulation of the primitive breast bud by testicular oestrogen or by oestrogen converted peripherally from testosterone. Alternatively, it is possible that testicular androgen secretion may inhibit breast development in boys.

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Correspondence to Dr J McKiernan, Paediatric Department, Regional Hospital, Wilton, Cork, Ireland.

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Salt loss in congenital adrenal hyperplasia due to 11 β-hydroxylase deficiency

Z HOCHBERG, A BENDERLY, AND Z ZADIK

Departments of Paediatrics, Rambam Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa and Kaplan Hospital, Rehovot, Israel

SUMMARY Nine patients with 11 β-hydroxylase deficiency had 13 episodes of gastroenteritis requiring hospital admission and fluid administration. Eight episodes were accompanied by hyponatraemia and salt loss. The salt losing patients were treated with excessive glucocorticoid and those with normal serum sodium concentrations were treated with inadequate glucocorticoid. Excessive glucocorticoid suppressed deoxycorticosteroid secretion, resulting in salt loss.

Five per cent of cases of congenital adrenal hyperplasia are due to 11 β-hydroxylase deficiency.[1] The disease is characterised clinically by virilisation and hypertension.[2 3] The enzymatic block results in low serum cortisol and aldosterone values and increased concentrations of 11-deoxycortisol and 11-deoxycorticosterone.[3–5] Increased concentrations of 11-deoxycorticosterone are believed to be responsible for sodium retention in these aldosterone deficient patients. We have previously shown that 11-deoxycorticosterone suppression by glucocorticoid treatment results in balanced salt loss.[6] The present study documents frequent episodes of salt loss in these patients during diarrhoeal disease.

Patients and methods

Data were collected retrospectively from the hospital records of 14 patients with 11 β-hydroxylase deficiency. Thirteen episodes of acute gastroenteritis were found in the records of nine patients. In all 13 episodes, gastroenteritis was severe enough to require hospital admission and intravenous or intragastric administration of fluid. This was given in all