Virilisation of female preterm infants

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Abstract

Two cases of hypertrophy of the clitoris in premature girls are reported; this was associated with persistently high concentrations of adrenal fetal zone androgens.

Isolated hypertrophy of the clitoris in neonates is known to be associated with congenital adrenal hyperplasia, administration of androgens to the mother in the second and third trimesters of pregnancy, and maternal androgen secreting tumours. We report two cases of progressive hypertrophy of the clitoris developing after birth, and associated with persistent excretion of high concentrations of 3β-OH-5-ene steroids, produced by the fetal adrenal zone and which are known to be weak androgens. This association has not previously been reported.

Case reports

CASE 1

A girl, birth weight 640 g, was one of twins delivered at 24 weeks' gestation for antepartum haemorrhage; the mother was aged 24, para 1+1. The second twin died aged 11 hours.

This study showed that interobserver variability did not exceed intraobserver variability in the measurement of pulsatility index using a duplex Doppler scanner. In some infants, however, measurements of pulsatility index varied widely, and it would therefore seem sensible not to make clinical judgments on a single pulsatility index estimate. This small study was confined to preterm infants, none of whom had a pulsatility index in the pathological range. Reproducibility of measurement of pulsatility indices over a wider range of normal and abnormal values should be established if the pulsatility index is to be used as a prognostic indicator.

drosterone sulphate (DHAS) was 6.8 µmol/l at 12 weeks and 2.5 µmol/l at 20 weeks. At 12 weeks plasma testosterone was 0.5 nmol/l. The results of serial 24 hour urinary steroid analysis using gas chromatography with capillary column2 are shown in the table.

Hydrocortisone 1.6 mg/kg/day was given from 13 weeks to 19 weeks on the advice of an endocrinologist because it was felt that congenital adrenal hyperplasia had not been ruled out at the time. At the age of 3 years, when she was admitted for surgical reduction of the clitoris, a 24 hour urinary steroid profile was normal, as were plasma DHAS and 17a-OH progesterone concentrations.

CASE 2
A girl, birth weight 1056 g, was born to a mother aged 36 years, para 2+3, who had had one neonatal death at 26 weeks. The pregnancy was complicated by vaginal blood loss and cervical dilation at 19 weeks. A cervical suture was inserted and labour suppressed with ritodrine and indomethacin. Maternal serology was positive for toxoplasmosis and she was treated with spiramycin. Premature rupture of membranes occurred at 22 weeks and there was spontaneous vaginal delivery at 27 weeks’ gestation.

The baby had mild respiratory distress requiring oxygen for three days, and was given benzylpenicillin and gentamicin; theophylline was given for apnoea. She was tube fed with expressed breast milk containing disodium hydrogen phosphate supplements. Additional sodium chloride was given for hyponatraemia. There was no clinical or serological evidence of congenital toxoplasmosis.

A large clitoris was noted at 6 weeks of age (fig 1B). Blood pressure was normal. Chromosomes showed a normal female karyotype. Plasma 17a-OH progesterone at 8 weeks was 22 nmol/l. The 24 hour urinary steroid excretion rates are shown in the table. Plasma ACTH was 10.3 pmol/l at 8 weeks and 10.1 pmol/l at 10 weeks. Cortisol concentrations ranged from <60 to 137 nmol/l.

She was discharged home at 8 weeks. Clitoromegaly gradually resolved over the next three months.

Discussion
Virilisation of female newborn infants is usually caused by excess androgen production due to an inborn error of steroid metabolism. This is not thought to be the cause in these two infants because the virilisation was not present at birth and urine steroid profiles showed no evidence of 21 or 11β-hydroxylase deficiency. Furthermore, plasma 17α-OH progesterone concentrations were not as high as those reported in congenital adrenal hyperplasia and were within the range reported for preterm infants without congenital adrenal hyperplasia.3 4

The plasma and urine measurements (table) show that both of these cases continued to excrete 3β-OH-5-ene steroids, which are weak androgens, long after the virilisation was first noticed, at concentrations which in term babies would only be found in the first few days of life.5 The persistence of the 3β-OH-5-ene steroids (mainly dehydroepiandrosterone (DHA) and its metabolites) in preterm infants has been described,4 but the association with virilisation of female infants has not. The cause of the persistent secretion of these fetal zone steroids has never been satisfactorily explained. There is evidence that ACTH regulates the adrenal cortex before and after birth, though other trophic factors may also be involved.6 In cell culture ACTH will stimulate fetal zone cells to produce DHA (and cortisol). In utero this DHA would be exported to the placenta and aromatised to oestrogens, a route of disposal not available to the infant after birth. The persistent 3β-OH-5-ene steroid excretion might be caused by excess ACTH drive, due for example, to

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**Table:** 24 hour urinary steroid excretion rates. The results from two full term infants and from two female preterm infants who were not virilised are given for comparison.

<table>
<thead>
<tr>
<th>Postnatal age (weeks)</th>
<th>Total cortisol metabolites (µg/kg/day)</th>
<th>3β-OH-5-ene metabolites (µg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>12</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1730</td>
</tr>
<tr>
<td>Case 2</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500</td>
</tr>
<tr>
<td>Preterm 1</td>
<td>9</td>
<td>220</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1410</td>
</tr>
<tr>
<td>Preterm 2</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>924</td>
</tr>
<tr>
<td>Term (n=2)</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130</td>
</tr>
</tbody>
</table>

**Figures:** Clitoromegaly in case 1(A) and case 2(B).
Inadequate cortisol synthesis secondary to diminished activity of \( \Delta^3 \) hydroxysteroid dehydrogenase. The concentrations of ACTH and of cortisol observed in the plasma, however, do not support this hypothesis. The persistent rise of the \( \Delta^3 \)-OH-5-ene steroids might therefore be due to the response of an adrenal cortex, consisting predominantly of DHA secreting fetal zone cells, to the normal ACTH drive required to maintain plasma cortisol concentrations.

It seems most likely that the weak fetal zone androgens are responsible for the virilisation. This cannot be the only cause however because both we (see table) and others have observed female preterm infants with raised concentrations of \( \Delta^3 \)-OH-5-ene steroids, who were not virilised. There may be other factors involved, for example variations in end organ sensitivity, localised conversion of fetal steroids to more potent androgens at the site of action in the genitalia, or high concentrations of circulating free androgens. Another factor may be the degree of immaturity of the preterm infant. Grumbach and Ducharme have pointed out that the virilising effect of an androgen depends on the maturity of the fetus. Androgen exposure between 8–13 weeks' gestation causes labial fusion and clitoromegaly, whereas after this time only hypertrophy of the clitoris is seen. The fact that the most severely affected infant was 24 weeks' gestation may be a manifestation of the different response of the immature fetus to weak androgens. The increasing survival of such immature infants is a recent phenomenon and this may be the reason why clitoromegaly has not been reported before in preterm babies.

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Topical prostaglandin \( E_2 \) gel for cervical ripening and closure of the ductus arteriosus in the newborn

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Abstract

The closure time of the ductus arteriosus was investigated in 29 full term babies born vaginally after induction with prostaglandin \( E_2 \) and in 22 controls. Serial Doppler echocardiography studies showed a significantly prolonged closure time in babies induced by prostaglandin \( E_2 \). Whether the difference is related to changes in fetal prostaglandin \( E_2 \) concentration remains to be established.

Patients and methods

Fifty one babies born at full term by vaginal delivery were studied. Twenty nine babies (mean (SD) gestational age 39.8 ± 6.6 weeks) were born to mothers who had received a 3 mg prostaglandin \( E_2 \) pessary (Upjohn) to ripen the cervix before induction of labour. Twenty two babies (mean (SD) gestational age 39.8 ± 1.4 weeks) whose mothers did not receive prostaglandin \( E_2 \) acted as controls.

Determination of ductal closure time

Serial Doppler echocardiography studies were done with an Aloka SSD-280S ultrasound scanner within 12 hours of birth, then twice daily at intervals of about 12 hours until ductal shunting could no longer be detected.

Measurement of maternal and cord prostaglandin \( E_2 \) concentrations

Cord blood was drawn from the umbilical vein immediately after clamping and cutting of the cord, and before placental separation. Paired maternal venous blood samples were collected at the same time. The samples were then transferred into prechilled polypropylene tubes containing EDTA and indomethacin, and cen-