Short reports

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A possible cause of glandular hypospadias in man

The incidence of hypospadias in the newborn male is low, being 3·3/1000 (*British Medical Journal*, 1972). The known causes of hypospadias are progestogen therapy given to the mother in early pregnancy and chromosome abnormalities in the neonate (Aarskog, 1970), but these account for only a small percentage of cases.

There is evidence from animal experiments that impaired or absent fetal testicular function affects the differentiation of the male external genitalia (Jost, 1953), while specific anti-androgen therapy can actually produce hypospadias in male rats (Neumann, Elger, and Steinbeck, 1969; Goldman *et al.*, 1972).

Plasma testosterone concentrations in human male and female fetuses of 12 to 18 weeks' gestation have been measured, and in the male fetuses the development of the urethra has been observed, thus allowing a correlation of the levels of plasma testosterone with the position of the urethral orifice.

Materials and methods

Umbilical cord blood was collected from male and female fetuses at 12 to 22 weeks' gestation, delivered at hysterotomy, by dividing the cord and allowing blood to drain from both ends. Care was taken to avoid

contamination with maternal blood or amniotic fluid. Plasma testosterone was measured by a radioimmunoassay method (Abramovich and Rowe, 1973) that showed minimal cross-reaction with those C₁₈, C₁₉, and C₂₁ steroids known to be present in human umbilical plasma.

The sex of the fetus was determined and the position of the urethral orifice in the male fetuses was examined using a hand lens or dissecting microscope where necessary.

Results

The amounts of plasma testosterone in male fetuses are shown in Table I and those from female fetuses in Table II. There are significant differences ($P < 0\cdot001$) between the mean levels in male and female fetuses of the ages 12 to 18 weeks. When the mean values of plasma testosterone in male fetuses are examined, they appear to stay high from 12 weeks to 18 weeks (crown-rump length 7–13 cm), but closer examination of the plasma levels in the youngest fetuses suggests that the plasma testosterone climbs from low levels in the youngest fetuses to reach peak levels which persist till about 18 weeks' gestation.

In the two youngest fetuses examined (gestational age 12 weeks, crown-rump length 7 cm, weight 19·5 g and 21·5 g), the testosterone concentrations were 84 ng/100 ml and 142 ng/100 ml, respectively, values lower than the mean levels found in the older fetuses.

TABLE I

Concentration of testosterone in umbilical cord plasma in male fetuses in mid-pregnancy

Gestational age (wk)	Fetal weight (g)	Crown-rump length (cm)	No. of fetuses	Mean testosterone concentration $\pm$ SD (ng/100 ml)	Range of testosterone concentration (ng/100 ml)
12–13	19·5–29·5	7–8	8	255 $\pm$ 99	84–379
13–15	33·5–67·5	8·1–10	10	235·5 $\pm$ 99	101–415
15–18	68–146	10·1–13	6	265 $\pm$ 90	184–378

TABLE II

Concentration of testosterone in umbilical cord plasma in female fetuses in mid-pregnancy

Gestational age (wk)	Fetal weight (g)	Crown-rump length (cm)	No. of fetuses	Mean testosterone concentration $\pm$ SD (ng/100 ml)	Range of testosterone concentration (ng/100 ml)
13–15	37–46·5	8–10	4	32 $\pm$ 28	11–67
15–18	66–153	10–13·5	6	26·5 $\pm$ 12	12–39

When the external genitalia of these two fetuses were examined, the urethral orifice was still on the under-surface of the penis, while in fetuses of crown-rump length of 8 cm it had approached the tip of the glans. The mean plasma testosterone concentration of the 6 fetuses with crown-rump length of 8 cm was 302 ng/100 ml, range 252–379 ng/100 ml. In fetuses of crown-rump length of 10 cm or longer, the urethral orifice appeared to be in the normal adult position. These results confirmed those of Glenister (1954).

Discussion

When the fetal plasma testosterone levels and the position of the urinary meatus are correlated it can be suggested that the transposition of the orifice to the tip of the penis is associated with rising levels of testosterone. On a fetus of 8 to 10 cm in crown-rump length when there is a reactive proliferation at the anterior extremity of the urethral plate (Glenister, 1954), the levels of testosterone are high and steady and drop well after the completion of the male external genitalia.

These findings do not prove that the positioning of the urinary meatus is dependent on fetal androgen levels in the human, as the high testosterone concentration and the transposition of the meatus may just be a coincidence in timing, but evidence from animal experiments using both anti-androgens and antiserum against testosterone suggests more than a close association.

Neumann *et al.* (1969), using the androgen antagonist cyproterone acetate in dog fetuses, found that the first sign of an androgen deficiency was the presence of hypospadias, while Goldman *et al.* (1972), who injected antiserum to testosterone into pregnant rats from 13 to 20 days of gestation, found that the male offspring had hypospadias. Thus it can be suggested in man that because high levels of testosterone are present in the fetus at the time of urethral formation, some cases of glandular hypospadias are caused by an androgen deficit. It is realized that this hypothesis may only apply to a small number of cases as a cause of hypospadias. It may well be that there is a lack of tissue response to normal levels of testosterone. Nevertheless, in the human this correlation of the high and rising androgen levels with the development of the urethra is reinforced by the available animal evidence.

Summary

Animal experiments strongly point to testosterone being implicated in the differentiation of the fetal male external genitalia. Plasma testosterone levels in human male fetuses are significantly higher than

those found in female fetuses just at the time of urethral formation in the male fetuses, suggesting that testosterone in the human may be implicated in the differentiation of the male external genitalia and that its lack may be important in some cases of glandular hypospadias.

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Iodide sialadenitis in childhood

Intravenous pyelography is frequently used in the investigation of renal disease in childhood. This is generally a safe procedure, though anaphylactic reactions may follow the intravenous injection of iodide (Tucker and Di Bagno, 1956). A rare occurrence, however, is painful swelling of sub-mandibular or parotid glands known as iodide sialadenitis. This has been reported previously in adults but not hitherto in children (Nakadar and Harris-Jones, 1971; Sussman and Miller, 1956).

Case report

An 8-year old girl presented with a 6-month history of intermittent right loin pain, dysuria, pyrexia, and vomiting. She was noted to be pale but examination was otherwise negative. Routine analysis of her urine showed no abnormality and culture was sterile. In view of her history she was admitted for further investigations. These showed Hb 12.9 g/100 ml, WBC 9200/mm³, erythrocyte sedimentation rate 15 mm/1st hour, urea 28 mg/100 ml, creatinine 0.6 mg/100 ml, uric acid 4.2 mg/100 ml. Serum electrolytes and plasma proteins were normal and her urine remained sterile.