**Background:** Fetal exposure to testosterone has been implicated in programming childhood behaviour, but little is known about the determinants of fetal testosterone concentrations.

**Aims:** To investigate the relation between fetal testosterone and maternal and fetal cortisol.

**Methods:** Clinically indicated blood samples taken from 44 human fetuses (mean gestational age 27 weeks, range 15–38), together with paired maternal samples, were analysed for testosterone and cortisol concentrations.

**Results:** Male fetuses had significantly higher concentrations of testosterone than females. Female but not male fetal concentrations rose significantly with gestational age. Fetal testosterone correlated positively with both fetal cortisol and maternal testosterone concentrations. Multiple regression showed that maternal testosterone and fetal cortisol were independently correlated with fetal plasma testosterone in both sexes.

**Conclusion:** Unlike the norm in the adult, where testosterone production is often inhibited by cortisol, in the fetus there is a positive link between the two.

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**METHODS**

**Experimental subjects**

Forty four women with pregnancies undergoing clinically indicated fetal blood sampling, and/or intrauterine blood/placental transfusion at the Centre for Fetal Care, Queen Charlotte’s and Chelsea Hospital, London, UK were recruited (mean gestational age 27 weeks, range 15–38). Twenty eight fetuses were normal; six had an anomalous karyotype (trisomy 18, n = 3; trisomy 21, n = 3) and 10 had some non-hydropic structural anomaly (abnormal heart, n = 5; anecephaly, n = 1; brain tumour, n = 1; ectodactyly, n = 1; IUGR, n = 2). Cortisol results from some of these fetuses have been reported previously. If samples were obtained from an individual fetus on more than one occasion, only the first was used. The sex of the fetus was known for 40 of these subjects.

The indications for fetal blood sampling were rapid karyotyping (n = 20) or suspected anaemia (n = 1), and for intrauterine transfusion, were fetal anaemia (n = 19), IUGR (n = 19) or thrombocytopenia (n = 4) in alloimmunised pregnancies. Eleven blood samples were collected at the placental cord insertion (PCI) and 33 at the intrahepatic vein (IHV). All baseline samples were collected prior to transfusion and within 10 minutes of needle entry, within which fetal cortisol concentrations are known not to rise. Neither fetal neuromuscular blockade nor analgesia was used. Mothers did not receive sedation. The purity of fetal samples was confirmed by comparison of fetal and maternal
mean corpuscular volumes and subsequent Kleihauer-Betke testing.

Ethical approval for the study was granted by the Hammersmith Hospitals Trust ethics committee, and written informed consent was obtained from all the mothers for the collection of additional blood samples for research purposes.

**Blood samples**

Following collection of clinical samples, up to 1–2 ml additional venous fetal blood was drawn into a syringe and placed in a chilled heparinised tube. Maternal blood (7 ml) was collected, when possible, by venepuncture into a heparinised Vacutainer (Becton Dickinson, Meylan Cedex, France) immediately before transabdominal needle insertion. Blood samples were spun in a refrigerated centrifuge at 3000 g for 15 minutes at 4 °C, to separate plasma, which was collected over ice and stored in aliquots at −80°C until subsequent batch assay.

**Assays**

Total plasma testosterone was assayed using a direct plasma radioimmunoassay (RIA) (DPC, Los Angeles, USA). The lower limit of sensitivity was 0.14 nmol/l, and the assay coefficient of variation 10.5%. Total cortisol concentrations were assayed using a standard solid phase RIA (DPC, Los Angeles, USA). The lower limit of sensitivity was 10 nmol/l and the assay coefficient of variation 5.3%. Maternal and fetal plasma sample pairs were analysed in the same assay run.

**Statistics**

Normally distributed data were analysed by standard parametric statistics using SPSS 10.0 for Windows (Chicago, IL), using paired or unpaired t tests or Pearson correlations as appropriate. Baseline fetal cortisol and testosterone and maternal testosterone and cortisol concentrations were all first normalised by ln transformation before any statistical analysis. The response to transfusion was analysed using δ (post-transfusion stress hormone concentration – pre-transfusion stress hormone concentration) values. Probability values are based on two tailed analysis unless stated otherwise.

**RESULTS**

Table 1 shows the plasma hormone concentrations for the whole sample. An initial univariate analysis showed that fetal plasma testosterone did not correlate with pH, pCO₂, or pO₂. There was no difference in these parameters, or in fetal testosterone or fetal cortisol whether the fetus was normal or anomalous (all by two tailed Student’s t test). The results from normal and anomalous fetuses were therefore combined for further analyses.

Male fetuses had significantly higher testosterone concentrations than females (p < 0.001) (fig 1). The gestational age range was similar in the two sexes: males, geometric mean 27 weeks, range 17–38 weeks; females, geometric mean 27 weeks, range, 20–36 weeks. Testosterone increased significantly in females with gestational age (r = 0.63, p < 0.01) but not in the males. Fetal cortisol was not significantly related to gestational age in either the males or females. With maternal cortisol and maternal testosterone, there was no significant relation with gestational age or difference with fetal sex.

There was no acute change in testosterone concentration after transfusion through either the IHV (mean pre- and post-transfusion, both 1.8 nmol/l, n = 14) or through the PCI (mean pre-transfusion 1.8 nmol/l, mean post-transfusion 1.7 nmol/l, n = 9). This was also found after a regression analysis adjusting for baseline fetal testosterone.

Table 2 shows the correlations between testosterone and cortisol in both fetus and mother.

The correlation between cortisol and testosterone in fetal plasma was positive (r = 0.407, p = 0.008). In contrast, maternal testosterone was not significantly correlated with maternal cortisol –0.032. Fetal plasma testosterone correlated positively with maternal concentrations (r = 0.414, p = 0.015) and maternal and fetal cortisol were also positively correlated (r = 0.526, p = 0.002). Similar patterns were observed for the male and female subgroups (all correlations greater than 0.4), but due to the smaller numbers not all were significant.

Multiple regression analysis was next used and showed that fetal sex, fetal cortisol, and maternal testosterone were all significantly and independently related to fetal plasma testosterone concentrations. In this analysis there was no contribution from maternal cortisol (table 3).

**DISCUSSION**

The main finding of this study is that, unlike the norm in the adult, there was a positive correlation between fetal cortisol and testosterone concentrations. Thus the mechanism of inter-related control of the HPA axis and testosterone production is different in the fetus compared with the adult.

As expected, we found that testosterone concentrations are higher in the male than the female fetus, although the differences were not large. This confirms previous results in amniotic fluid₂⁵ ᵃ and cord blood.₂⁶ We also found that there was a positive relation with gestational age in female but not male fetuses. This also confirms previous findings. Beck-Peccoz and colleagues₂⁰ have reported, as we show here (fig 1), that by term, concentrations are similar in the two sexes.
sexes, although they measured free rather than total testosterone. However the large majority of our sample (only one below 20 weeks) were in the second half of gestation, and there may be a surge of testosterone earlier than this in the males.

The positive correlation between cortisol and testosterone may be because fetal testosterone is produced partially in the adrenal, and like cortisol is, at least in part, under control of ACTH. In addition, Smith and colleagues have shown that placental corticotropin releasing hormone (CRH) promotes fetal adrenal secretion of DHEA-S, and have identified CRH receptors in fetal adrenal tissue. It is thus also possible that placental CRH induces fetal DHEA-S and this in turn is a precursor for testosterone. With the limited volume of the fetal blood samples, we were strictly limited in what we could study, and were not able to measure DHEA-S directly. It would also be of interest to measure the concentrations of the steroid binding proteins, which affect the amount of free steroid available. Fetal cortisol would also be relevant, as a steroid available. Fetal cortisone would also be relevant, as a precursor for testosterone. With the limited volume of the placenta, it is also possible that both are under joint or similar control.

Cortisol and testosterone in the fetus are clearly not under identical control; there are likely to be several different determinants of fetal testosterone concentrations. Whereas there was an increase in testosterone with gestational age in females, there was no such increase in cortisol over this age range. Also, unlike the case in our previous studies with cortisol, we found no acute increase in testosterone after transfusions that involved piercing the fetal abdomen at the IHV. If there is some joint control by ACTH it must have a different time course.

The positive correlation shown here between maternal and fetal testosterone concentrations is similar to that which we have previously found with cortisol. Both are liposoluble steroids that would be expected to cross the placenta readily. This is different from the case with β-endorphin or noradrenaline, which are not lipophilic and for which we have found no correlation between mother and fetus. With cortisol, maternal plasma concentrations are about 11-fold higher than fetal concentrations; with testosterone the concentrations found here in the two compartments were similar. This may reflect active metabolism of cortisol in the placenta by 11β-hydroxysteroid dehydrogenase (11β-HSD 2). More research is clearly needed to disentangle the pathways involved.

Table 2  Pearson correlations between maternal and fetal cortisol and testosterone concentrations (all analyses were carried out with the ln transformed values)

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A multiple regression analysis for fetal testosterone (ln) as dependent variable

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Although the testosterone did not show an acute rise in response to stress, the positive correlation between fetal cortisol and testosterone concentrations suggests that some of the factors that cause raised fetal cortisol concentration may also cause an increase in testosterone concentration. This in turn may influence fetal development in ways associated with a more masculine profile.

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There is no specific treatment, and long term follow up is indicated with associated abnormalities.

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Special Care Baby Unit, Royal Hospital, Muscat, Oman; maniokoth@omantel.net.om
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REFERENCES

IMAGES IN NEONATAL MEDICINE

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Figure 1 Photograph showing generalised cutis marmorata, dilated superficial veins, and telangiectasia involving the trunk and limbs. Consent for this figure was obtained from the patient’s parents.
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Arch Dis Child Fetal Neonatal Ed 2005 90: F169
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