

## SHORT REPORT

## Reduced birth weight in boys with hypospadias: an index of androgen dysfunction?

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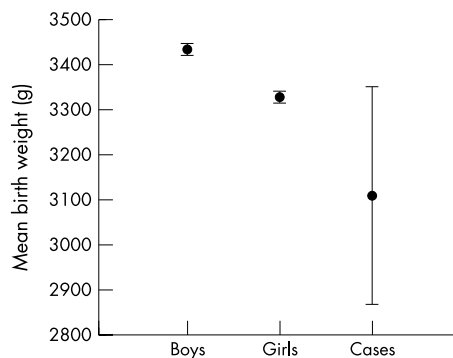
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Anthropometric birth measurements analysed for 51 boys with hypospadias identified in a prospective cohort study showed significant reductions in mean values for birth weight, length, and head circumference compared with controls. The absence of the usual sex dimorphism for these variables suggests that the results represent a marker of fetal androgen dysfunction in this subgroup of infants.

Isolated hypospadias represents a less severe abnormality in male sex differentiation and is not associated with sex reversal. However, it is the commonest congenital malformation in the male infant, with an estimated prevalence of 1–2 per 1000 live male births.<sup>1</sup> We have recently reported a higher proportion of boys with hypospadias born to mothers who were vegetarian during pregnancy.<sup>2</sup> We here report anthropometric birth measurements in 51 boys with hypospadias to determine whether reduced growth may be a surrogate marker of fetal androgen dysfunction in this group of undermasculinised males.

## METHODS

The cases of hypospadias were identified through the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective cohort study investigating environmental and other



**Figure 1** Mean birth weight (95% confidence interval) for boys, girls, and boys with hypospadias (cases).

influences on the health and development of children<sup>3</sup> (website: <http://www.ich.bris.ac.uk/ALSPACext/Default.html>). Pregnant women resident in the three Bristol based health districts of Avon in South West England with an expected date of delivery between 1 April 1991 and 31 December 1992 were eligible for the study. A total of 7928 boys were born to women enrolled in the study.

Several methods were used to identify cases of hypospadias: (a) maternal report from postal questionnaires completed annually for the first 3 years of life, detailing reasons for medical referral and any surgery; (b) birth notifications; (c) newborn examination records; (d) post mortem reports.

Birth weights measured to the nearest gramme were recorded in the delivery room. The average birth weight in cases of hypospadias was compared with that for the remainder of the male ALSPAC sample using *t* tests. Adjustment was made for gestational age using multiple regression.

## RESULTS

Within the ALSPAC sample of 7928 boys, there were 51 cases of hypospadias giving an overall prevalence of 6.4 per 1000 male births, a figure considerably higher than generally quoted.<sup>1</sup>

Their mean birth weight was 3108 g compared with 3433 g for the remaining 7839 boys for whom birth weight was available ( $p < 0.0001$ ). The mean birth weight for girls in the ALSPAC sample ( $n = 7393$ ) was 3327 g (fig 1). Significant differences were still observed for birth weight after adjustment for gestational age (table 1). There was also a significantly larger proportion of hypospadias cases with birth weight less than 2500 g: 19.6% compared with 5.5% of the remaining boys and 6.0% of girls ( $p < 0.0001$ ).

Data on birth length and head circumference were similarly analysed (table 1). Numbers were fewer for these variables in both control and hypospadias cases. Nevertheless, birth length and head circumference measurements were significantly less in boys with hypospadias than the control group of boys, even after adjustment for gestation.

## DISCUSSION

The mean birth weight in this cohort of boys with hypospadias was reduced by more than 300 g compared with control boys and was even lower than that of the girls. A significantly

**Table 1** Means (95% confidence intervals) for birth weight, birth length, and head circumference for boys without hypospadias, and girls and boys with hypospadias, after adjustment for gestation

	Birth weight (g)	Birth length (cm)	Head circumference (cm)
Boys	3446 (3436 to 3456)	50.9 (50.9 to 50.9)	35.2 (35.1 to 35.2)
Girls	3313 (3302 to 3323)	50.0 (49.9 to 50.1)	34.4 (34.4 to 34.5)
Hypospadias cases	3220 (3093 to 3348)	50.1 (49.5 to 50.8)	34.6 (34.2 to 34.9)
p Value	< 0.0001	< 0.0001	< 0.0001

higher proportion of the hypospadias boys were of low birth weight. This implies that either factors underlying the cause of hypospadias in these infants are also more likely to result in fetal growth retardation or the growth retarded fetus is more susceptible to influences that can cause hypospadias. However, differentiation of the external genitalia in the male is usually complete by the second trimester whereas the inhibiting effects on somatic growth may not manifest until later in gestation. The small increment in birth length and head circumference in male compared with female infants was also negated in the hypospadias group. Similar results have been reported in hitherto unexplained male undermasculinisation.<sup>4 5</sup>

These results suggest that isolated hypospadias of unknown cause may be related to factors that adversely affect optimal androgen function during male fetal development. Mean birth weight is also reduced in genetic males with androgen insensitivity, a syndrome of sex reversal caused by resistance to the action of androgens.<sup>6</sup> We have recently reported an association between hypospadias and a variable number of glutamine repeats in the androgen receptor which may play a causative role in mild genital anomalies of an unknown multifactorial origin.<sup>7 8</sup> There is evidence from in vitro studies that polyglutamine variants can alter transcriptional activity of the androgen receptor.

The ALSPAC study has uniquely highlighted a possible environmental link with the risk of an infant born with hypospadias.<sup>2</sup> Several coordinated genetic products are essential to ensure an optimal production and action of androgens during the critical period for fetal male sex differentiation. There is compelling evidence that the sex dimorphism in birth size is, at least in part, related to androgens in addition to perhaps some unknown influence of the Y chromosome. There are a number of polymorphic variants in a range of gene products involved in androgen biogenesis. Cumulatively, these may contribute to a suboptimal androgenic effect, the result compounded perhaps by adverse environmental factors operating as endocrine disruptors. The increased prevalence of hypospadias in this study compared with previous reports does add weight to that hypothesis, although the difference may also be partly due to more accurate case ascertainment. There is now the opportunity to study this hypothesis further through the unique resource provided by the ALSPAC study.

## ACKNOWLEDGEMENTS

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