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Shorter anogenital and anoscrotal distances correlate with the severity of hypospadias: A prospective study

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Summary

Introduction
Anogenital distance (AGD) is a recognised marker of *in utero* androgen action.

Objective
This study aimed to evaluate the relationship between severity of hypospadias and AGD.

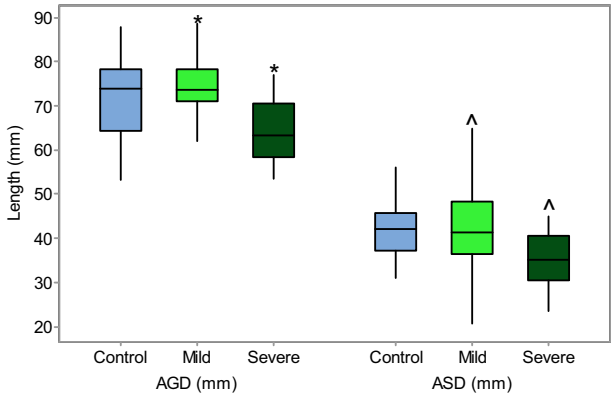
Study design
Boys undergoing hypospadias repair in a single tertiary centre between May 2012 and February 16 were included in the study. Anogenital distance was measured from the centre of the anus to the base of the penis, and anoscrotal distance (ASD) from the centre of the anus to the junction between the smooth perineal skin and scrotal skin. Trained paediatric urologists made all measurements using digital callipers.

Results
Fifty-nine boys with hypospadias and 31 age-matched controls undergoing circumcision (median age 1.37 years, range 1.01–1.96) had AGD and ASD measured under anaesthetic. The patients were divided into two groups, according to hypospadias severity: group 1 – distal penile/subcoronal/glandular ($n = 40$); and group 2 – perineal/penoscrotal/midshaft ($n = 19$). The median AGD for controls was 74.0 mm (range 53.2–87.8) and for hypospadias it was 72.3 mm (range 50.7–90.0) ($P = 0.816$). The median ASD for controls was 42.3 mm (range 31.0–56.1) and for hypospadias it was 39.4 mm (range 20.7–77.0) ($P = 0.224$).

Considering severity of hypospadias, the median AGD for group 1 and group 2 was 73.7 mm (range 50.7–90.0) and 63.3 mm (range 53.6–77.0), respectively ($P < 0.001$). The median ASD was also higher in group 1, at 41.3 mm (range 20.7–65.0), compared to 35.2 mm (range 23.5–77.0) in group 2 ($P = 0.119$) (Summary Fig.).

Discussion
This study showed that more severe forms of hypospadias are associated with shorter AGD and ASD. These findings agree with two previous studies that identified reduced AGD in boys with hypospadias. However, these studies did not investigate an association with severity of hypospadias. As hypospadias is multifactorial, only a small proportion of cases are thought to be associated with impaired *in utero* androgen exposure. The shorter AGD in boys with severe hypospadias compared with mild hypospadias would indicate that AGD is a marker of the severity of androgen production. This may also suggest that less severe forms of hypospadias have a different aetiology involving a later stage of development, and that they are not the result of reduced androgen exposure in the male programming window between the 8–14 weeks gestation.

Conclusion
This study identified that boys with more severe hypospadias are more likely to have a shorter AGD and ASD than boys with mild hypospadias. This may indicate that there is a more profound impairment of *in utero* androgen action in severe hypospadias.



Summary Fig. Anogenital and anoscrotal distances according to hypospadias severity. AGD, anogenital distance; ASD, anoscrotal distance. Mild = glandular, coronal or distal penile hypospadias; Severe = mid-shaft, penoscrotal or perineal hypospadias. *Severely shorter compared with mild, $P < 0.001$. ^Severe trend towards being shorter compared with mild, $P = 0.119$.

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Introduction

Hypospadias is one of the most commonly reported congenital abnormalities in boys, with an incidence of around 3/1000 live births [1], which is believed to be increasing [2,3]. Yet its aetiology remains unclear and is likely to be multi-factorial. Implicated factors may be foetal, placental or maternal; they include low birth weight, recognised syndromes and single gene mutations, placental insufficiency, gestational endocrine disruptor exposure, and increasing maternal age [4]. One documented factor in the development of hypospadias is reduced antenatal exposure to testosterone during the masculinisation-programming window (MPW) [5]. The MPW is a time period from gestational days 15–18 in rats, which is equivalent to 8–14 weeks gestation in humans [6], during which adequate foetal androgen action is essential for the later development of the male genitalia, including normal penis length and volume, and testicular descent [7].

In rodents, measurement of the postnatal anogenital distance (AGD) provides a valuable marker of antenatal androgen exposure and action [8]. In humans, this has been found to be associated with exposure to particular endocrine-disrupting chemicals [9] and thus, may represent a surrogate marker of *in utero* androgen exposure. Reports have also linked reduced AGD with hypospadias [10], cryptorchidism [11], and impaired male fertility [12]. These conditions have been considered to be part of a spectrum of disease under the term testicular dysgenesis syndrome (TDS), which is proposed to be the result of reduced androgen action *in utero*, possibly due to exposure to endocrine disruptors [13]. While it has been found that boys with hypospadias have shorter AGD than those who do not, a potential linear relationship between degree of androgen exposure and severity of hypospadias has not yet been investigated. It is still unclear whether there is a critical threshold for androgen exposure above which genital development is normal, or whether there is an exposure-response relationship whereby, as androgen exposure approaches normal, hypospadias becomes less severe. This study was designed to assess the relationship of AGD and ASD with the severity of hypospadias.

Material and methods

Boys undergoing hypospadias surgery, aged <2 years old, between May 2012 and Feb 2016 were included in the study as long as the operating surgeon was available to make measurements immediately prior to commencing surgery. The AGD and ASD were also measured in boys with no congenital anomalies, but undergoing circumcision in the operating theatre, who acted as age-matched controls. The study was discussed with the local ethics committee who advised that formal ethics review was not required. Two consecutive measurements of AGD and ASD were obtained at the time of hypospadias surgery by trained paediatric urologists, and the average was used for comparison. All measurements were made using digital callipers (Oxford Precision, Leicester, England) while the patient was under general anaesthetic. The ASD was measured from the centre of the anus to the junction between the smooth perineal skin and skin of the scrotum (Fig. 1). The AGD was measured from the centre of the anus to the base of the penis (Fig. 1). The operating surgeon recorded hypospadias severity, both pre-operatively and after degloving, in case of discrepancy by indicating meatal position on a diagram. Hypospadias severity was classed as one of six categories: glandular, coronal, distal penile, mid-shaft, penoscrotal or perineal. At the time of surgery, information on current age, weight and height was collected.

A separate member of the study team, who was blind to the patients' hypospadias severity, reviewed the medical notes, the AGD and ASD measurements at a later date. Data were collected on gestational age at birth, birth weight, and presence of any additional medical conditions.

Age-specific standard deviation score (SDS) for current weight and birth weight were calculated by comparison with UK normative data [14]. Birth weight calculations were adjusted for gestational age at birth. For analysis, hypospadias severity was categorised as group 1 (mid-shaft, penoscrotal, perineal) or group 2 (glandular, coronal, distal penile). Normality of data was assessed using the Anderson–Darling test. Differences were analysed using the Mann–Whitney test for non-normally distributed data. Spearman's rank correlation was calculated for non-continuous data (Minitab 16 Statistical Software, 2013, State College, PA: Minitab, Inc). Data were expressed as median (range minimum to maximum).

Results

Data and measurements were collected for 59 boys with hypospadias and 31 controls. Of the 59 boys with hypospadias, 11 (19%) cases had additional genital anomalies. These comprised seven cases of chordee, two unilateral undescended testis, one case of chordee associated with bifid scrotum, and one case of micropenis with penoscrotal fusion. None of the boys undergoing circumcision had any associated anomaly.

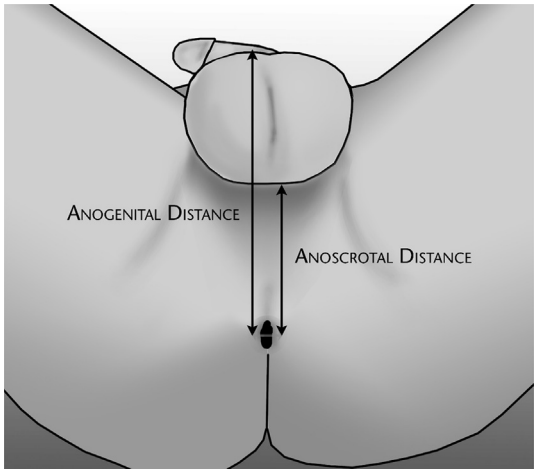

Figure 1 Measurement of anogenital and anoscrotal distances.

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