Long-term outcomes of hypospadias: Urological and psychosexual function and endocrine-reproductive capacity

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Background

Male genital development is a complex process requiring the intricate and delicate interaction of genetic, hormonal and mechanical factors. It is therefore unsurprising that male genital development frequently hampers, commonly presenting with some form of hypospadias. Although roughly 1/200 newborn males is born with hypospadias, very little is known regarding their long-term outcomes (1). This gap in knowledge renders surgical, endocrine, fertility and genetic counseling of patients and parents difficult. Performing long-term outcome studies is therefore imperative to be able to provide tailored follow-up and guidance to men born with hypospadias and their parents.

Methodology

The main aim of this PhD thesis was to explore the outcome of children and young men born with various forms of non-syndromic hypospadias and elucidate the genetic factors underlying the development of hypospadias. A first, cross-sectional study was performed exploring the psychosexual, urological, endocrine outcome and seminal parameters of adolescent and young adult men (AYA) born with non-syndromic hypospadias compared to healthy, male peers. In total, 193 hypospadias cases and 50 typical males, all aged 16-21 years, were recruited in Ghent university hospital and medical university Vienna. DNA samples were obtained for in depth genetic tests in cases with familial or severe hypospadias or those with a suboptimal endocrine or reproductive outcome (n=99). These data were supplemented by a second, retrospective study focusing on the endocrine outcome of children and adolescents with severe forms of hypospadias, differentiating between boys born small for gestational age (SGA; n=115) and boys born appropriate for gestational age (AGA; n=64). Data were obtained from twelve DSD-reference centers from across the world through the I-DSD consortium (www.i-dsd.org). Lastly, a prospective collection of foreskin samples obtained through routine hypospadias repair (n=197) and circumcision (n=198) was used to compare androgen receptor expression in Dartos tissue.

Results

The overall psychosexual outcome of AYA who underwent childhood hypospadias repair was suboptimal, but overall not different from male peers (2). Several risk factors were associated with impaired psychosexual outcomes, such as the severity of hypospadias, need for multiple penile surgeries and dissatisfaction regarding genital appearance. Nonetheless, the vast majority of patients were happy they had underwent the hypospadias repair during their childhood and experienced a positive attitude towards the current practice of childhood surgery. Regardless of the sometimes suboptimal esthetic outcome, as assessed by a physician, only two men (1%) had received negative comments from their sexual partners. Of note, in both cases the comments were restricted to penile size and were not based on the overall esthetics of the genital appearance (e.g. scar tissue, curvature, penile axis). Patients rated the esthetic outcome of their genitals overall better than the physician and were often not bothered by esthetic and functional imperfections. Mild erectile dysfunction and a wide range of ejaculatory problems were reported in 11.2% and 12% of AYA, respectively. Both the erectile dysfunction and ejaculatory problems were unrelated to patient or surgical factors and thus likely caused by underlying psychosexual factors. Based on these data, we would recommend a restrictive attitude towards re-interventions for non-functional problems. Furthermore, psychosexual counseling could also benefit the well-being of men born with hypospadias, especially in those with severe forms or when repeated penile surgeries are needed. Although the majority of patients and parents had remained positive towards the childhood hypospadias repair, many parents indicated that they had experienced the entire diagnostic and therapeutic process as very stressful. Early psychological support may thus be helpful for some parents of boys born with hypospadias.

Regarding the surgical and urological outcome, we discovered a surgical re-intervention rate of 39.2% of those who had their first hypospadias repair in Ghent university hospital or medical university Vienna, thus excluding those who were referred for failed surgery from a different center (3). Suboptimal urinary and/or sexual outcomes were found in 52.9% of cases, with 24.9% of the AYA having residual hypospadias and 5.7% having a fistula at the time of the study. Of note, these boys were not actively seeking medical counseling for these problems. Taking into account that these complications sometimes arose many years after the first hypospadias repair, we recommend the organization of urological follow-up for decades after the initial surgery. Furthermore, our data support the organization of a specialized urology team for hypospadias repair and deferral of hypospadias repair until the age of at least 12 months, as this could reduce the complication rate. Smaller adult stretched penile lengths and more severe hypospadias were also associated with worse outcomes and warrant a cautious surgical approach.

In 2001, Skakkebaek et al. (4) postulated that hypospadias, cryptorchidism, male infertility and testicular cancer are part of a spectrum with a common etiology. This testicular dysgenesis syndrome hypothesis has since then been supported by several studies. However, very little is known about the position of hypospadias within this spectrum. In our studies, we discovered subclinical Leydig cell dysfunction in childhood and young adulthood, with very few boys having encountered problems regarding their pubertal devel-

opment (5). Similarly, clinically relevant hypogonadism was not found in any of the cases of our cross-sectional study, even in those with profound undervirilisation (Tack LJW, EBioMedicine, in press). However, spermatogenesis was a major concern. Low sperm concentrations were common in men born with severe and complex forms of hypospadias and men born small for gestational age. Remarkably, in men born SGA with hypospadias, the severity of hypospadias and overall severity of undervirilisation were unrelated to the risk of having reduced sperm concentrations. This group of men was also found to have poor growth, with approximately 30% having insufficient catch-up growth and 35% not reaching their target height based on mid-parental height. In the overall SGA population, poor catch-up growth and short stature are expected in 10% of cases (6). Therefore, referral to the pediatric endocrinologist is warranted in all SGA children born with hypospadias for follow-up of growth and if needed, initiating growth hormone treatment. Given that sub- and infertility were common in our cohort, we recommend discussing potential fertility issues during follow-up once the patient is deemed mature enough. If the patient is willing, he should be offered fertility assessment through semen analysis. Hormone assays using FSH or inhibin B were found unreliable markers to screen for potential sub- or infertility as the majority of men with low sperm concentrations would be missed when using the laboratory cut-off values. However, with careful counseling, most adult men (94.5%) were found to be willing to provide a semen sample which will yield direct evidence of impaired spermatogenesis. How the semen characteristics will evolve with the aging individual and which boys should opt for cryopreservation remains a point of debate and should be determined based on future studies.

In the final part of the PhD project, the underlying mechanisms in the development of hypospadias were sought. Androgen receptor expression in foreskin samples was found not to be different between boys born with hypospadias, versus healthy controls (7). Instead, age was found to be the principle determinant of androgen receptor expression, correlating with the phases in life during which there are high androgen levels (i.e. minipuberty and puberty). Although we failed to find differences in AR expression, these data do not exclude impaired androgen receptor functionality or downstream defects. Based on our data, when exploring the role of the androgen receptor in the development of hypospadias, strict age matching appears to be crucial. In-depth genetic tests were performed using whole exome sequencing to assess monogenic causes of hypospadias as well as oligenic variant combinations using the Oligogenic Resource for Variant AnaLysis (ORVAL) online platform (8). No monogenic variants or oligogenic variant combinations were found to be (likely) pathogenic as only variants of unknown significance were withheld. These findings suggest a multifactorial origin of hypospadias in which environmental and placental factors could play an important role as demonstrated by the higher incidence of hypospadias in SGA boys (9). We therefore do not recommend routine use of resource consuming gene panel testing, even in severe forms of hypospadias unless if an underlying syndrome is suspected.

Conclusion

Most men born with hypospadias are satisfied with their urogenital outcome and support childhood hypospadias surgery. As a result, the psychosexual outcome of this group of men is generally not diminished compared to typical male peers. Nonetheless, complications following hypospadias repair are very common. They can arise long after the initial surgery, and can impact the psychosexual and urogenital outcome. Therefore, current practice should be optimized, and urological post-surgical follow-up during decades is recommended, including sometimes psychological guidance to some patients and sometimes their parents. Furthermore, multidisciplinary management of boys born with hypospadias is needed as growth and spermatogenesis are a major point of concern in some subgroups of men born with hypospadias. The exact cause of hypospadias remains elusive but is likely multifactorial and warrants further studies.

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Figure 1 : *Summary of recommendations for the follow-up of boys/men born with hypospadias.*