

Hypospadias Surgery

- **long-term outcome focusing on adolescence**

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UNIVERSITY OF GOTHENBURG

Gothenburg 2018

Cover illustration: Tulips (with different 'curvatures')
by artist Meg Ersbacken-Engman, Avesta.

Hypospadias Surgery – long-term outcome focusing on adolescence
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ISBN 978-91-629-0462-3 (PRINT)
ISBN 978-91-629-0463-0 (PDF)

Printed in Gothenburg, Sweden 2018
Printed by BrandFactory

“Det blir bättre framåt kvällen
skrev en eftertänksam vän.

Dagen ställer stora krav.
Ingenting man tänkt blev av.

Men mot kvällningen i stillhet
blir man nästan som förbytt.

Då, när inget märkbart händer
lever man på nytt.”

~ Brita af Geijerstam

To my family

Hypospadias Surgery

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ABSTRACT

Hypospadias is a malformation that affects 1/125 newborn boys in Sweden. 1/10 with hypospadias are born with the most severe form; proximal hypospadias. The treatment, which is surgical, is performed during the first years of life. The aim of this thesis was to evaluate the urological, psychosocial and psychosexual outcomes in adolescence among boys and young men after surgery for different degrees of hypospadias.

Study 1 showed that the flow rates of boys with distal to midpenile hypospadias operated with the Tubularized Incised Plate (TIP) procedure (introduced in 1994) improved spontaneously in puberty compared to the obstructive flows in childhood. The hypoplastic urethral plate used at TIP seems to grow with the boy sufficiently to provide a good urinary flow in puberty and a continuously straight penis.

Study 2 investigated psychosocial outcomes in adult men with different degrees of hypospadias and showed that Psychological General Well-Being (PGBW) was comparable to controls, patients treated for hypospadias had a good hrQoL and can be expected to have a normal psychosocial life with partners and children to the same extent as controls, but repeated follow-up and support during childhood/adolescence is important for patients with proximal hypospadias.

Study 3 showed that the uroflows improved also for patients with proximal hypospadias in adolescence. Glanular sensation was normal in 72% and 18% had some degree of penile curvature in adolescence. Many patients were dissatisfied with penile length and many, in particular patients reconstructed with the Duckett procedure, required reoperations. One third of patients requiring reoperations were reoperated more than 10 years after primary surgery, stressing the need of followup beyond puberty.

Study 4 investigated the psychosocial and psychosexual outcome for patients with proximal hypospadias in comparison with distal hypospadias and controls and found that despite concerns about penile length in the group of

patients with proximal hypospadias, sexual experiences were comparable to both patients with distal hypospadias and controls. However, more than a third of patients with proximal hypospadias expressed uncertainty in questions related to physical contact. Specialized tutoring in school was also more common in patients with proximal hypospadias. Continued follow-up through adolescence, with extra time offered for age-adequate information and support is important.

In conclusion, urinary, psychosocial and psychosexual outcome in adolescence is good for patients with distal and proximal hypospadias, but the latter may require a considerable amount of reoperations to achieve this. Hypospadias patients are concerned with penile length and especially patients with proximal hypospadias are in need of more support which is preferably given during urological follow-up.

Keywords: hypospadias, outcome, long-term follow-up, adolescence

ISBN 978-91-629-0462-3 (PRINT)

ISBN 978-91-629-0463-0 (PDF)

<http://hdl.handle.net/2077/55390>

SAMMANFATTNING PÅ SVENSKA

Hypospadi är en missbildning som drabbar 1/125 födda pojkar i Sverige. Cirka en tiondel av pojkarna föds med den svåraste formen: proximal hypospadi. Behandlingen, som är kirurgisk sker under småbarnsåren. Operationen syftar till att förlänga urinröret och räta upp penis och målen är en god urologisk och sexuell funktion samt en god kosmetik. Målet med denna avhandling var att utvärdera utfallet urologiskt, psykosocialt och psykosexuellt hos unga män och pojkar i adolescensen opererade för olika grader av hypospadi.

Studie 1 visade att urinflödet hos pojkar opererade med Tubularized Incised Plate (TIP), för distal till midpenil hypospadi, förbättrades spontant i de flesta fall i puberteten jämfört med de obstruktiva flödena i barndomen. Den hypoplastiska urinrörspattan som används vid TIP, tycks växa med individen och tillväxa adekvat för att kunna ge ett bra flöde i puberteten och en fortsatt rak penis.

Studie 2 visade att Psychological General Well-Being (PGWB) hos vuxna män med olika grader av hypospadi var jämförbart med kontroller. Vi fann ingen skillnad i andel som var gifta, antal barn i familjen, arbete eller upplevelse av mobbing. Gruppen med proximal hypospadi önskade mer uppföljning och tenderade att undvika relationer på grund av rädsla att bli sårade. Patienter opererade för hypospadi har en god hrQoL, kan förväntas ha ett normalt psykosocialt liv med partner och barn i samma utsträckning som kontroller men fortlöpande uppföljning och stöd är viktigt för patienter med proximal hypospadi.

Studie 3 undersökte det urologiska resultatet hos ungdomar födda med proximal hypospadi och opererade i Göteborg. Resultaten visade att urinflödena var förbättrade i tonåren, känslan på ollonet var normal hos 72% and 18% hade någon grad av kurvatur på penis. Många, speciellt de opererade med Duckett, hade behövt reoperationer. En tredjedel reopererades mer än 10 år efter första operationen vilket visar på behovet att följa dessa patienter förbi genomgången pubertet.

Studie 4 undersökte psykosociala, psykosexuella resultat och sexuell funktionen hos patienter med proximal hypospadi jämfört med patienter med distal hypospadi och kontroller. Resultaten visade att trots oro för penislängden hos ungdomar med proximal hypospadi, var de sexuella erfarenheterna jämförbara med båda kontrollgrupperna. Däremot uttryckte mer än en tredjedel av patienter med proximal hypospadi osäkerhet kring frågor rörande kroppskontakt. Extra stödinsatser i skolan var också vanligare hos patienter med proximal hypospadi. Vi rekommenderar därför fortsatt

uppföljning genom uppväxten där extra resurser erbjuds för åldersadekvat information och stöd.

Sammanfattningsvis talar resultatet av dessa studier för att patienter med både distal och proximal hypospadi har goda långtidsresultat avseende urologisk funktion, psykosocialt utfall och psychosexuell utveckling. Framför allt för patienter med proximal hypospadi kan det krävas flera reoperationer för att uppnå ett gott resultat. Patienter med hypospadi är mer missnöjda med penislängd, men lika nöjda med penis övriga utseende jämfört med kontroller. I synnerhet patienter med proximal hypospadi behöver fortlöpande uppföljning för att stödja en normal psychosexuell utveckling och för att upptäcka sena komplikationer.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. **Andersson M**, Doroszkiewicz M, Arfwidsson C, Abrahamsson K, Holmdahl G. Normalized Urinary Flow at Puberty after Tubularized Incised Plate Uretroplasty for Hypospadias in Childhood. *J Urol* 2015 (194) 1407-1413.
- II. Örtqvist L, **Andersson M**, Strandqvist A, Nordenström A, Frisé L, Holmdahl G, Nordenskjöld A. Psychosocial outcome in adult men born with hypospadias. *J Pediatr Urol*. 2017 Feb;13(1):79.e1-79.e7.
- III. **Andersson M**, Sjöström S, Doroszkiewicz M, Örtqvist L, Holmdahl G. Urological outcome in adolescents after surgery for proximal hypospadias in childhood. Manuscript. Submitted.
- IV. **Andersson M**, Sjöström S, Wängqvist M, Örtqvist L, Nordenskjöld A, Holmdahl G. Psychosocial and sexual outcome in adolescents after surgery for proximal hypospadias in childhood. Manuscript. Submitted.

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ABBREVIATIONS

AR	Androgen receptor
AMH	Anti Müllerian Hormone
BC	Bladder Capacity
BESAA	Body Esteem Scale for Adults and Adolescents
CAH	Congenital Adrenal Hyperplasia
CAIS	Complete Androgen Insensitivity Syndrome
CRF	Clinical Report Form
DHT	Di Hydro Testosterone
DoH	Declaration of Helsinki
DSD	Disorders of Sex Development
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
hCG	Human chorionic gonadotropin
HOSE	Hypospadias Objective Scoring Evaluation
hrQoL	Health Related Quality of Life
IVF	In Vitro Fertilization
LS	Lichen Sclerosus
LUTS	Lower Urinary Tract Symptoms
Md	Median
PAIS	Partial Androgen Insensitivity Syndrome

PGWB	Psychological General Well Being
PPS /PPPS	Penile Perception Score / Pediatric PPS
PVR	Post Void Residuals
SGA	Small for Gestational Age
SPR	Swedish Population Register
SRY	Sex Determining Region Y
TDS	Testicular Dysgenesis Syndrome
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
WHO	World Health Organization

DEFINITIONS IN SHORT

Androgens	Male sex hormones
Cryptorchidism	One or both testicles not situated in the scrotum
Hypospadias	Penile malformation with an urethral opening somewhere between the tip and the scrotum
Likert Scale	Bipolar ranking scale. The two ends on the scale represent opposite positions of opinion
Micropenis	Smaller than 2.5 standard deviations less than the average, or ≤ 2.5 cm in a newborn.
Oligohydramnios	A deficiency of amniotic fluid during pregnancy
Penile curvature	An abnormal bend down-wards of the penis observed at erection
Phenotype	Physical traits expressed in an individual
Phimosis	A narrowing of the foreskin making retraction over the glans difficult or impossible

THESIS AT A GLANCE

Paper	AIM	DESIGN/ METHOD	RESULTS	CONCLUSION
I	To evaluate uroflow results in puberty after TIP repair.	Prospective longitudinal cohort study comparing uroflow results from 40 patients operated with TIP repair after 1 year, 7 years and in puberty.	Uroflows that were obstructive in 56% of cases at 1 year were normalized. In puberty only 5% were considered obstructive.	The hypoplastic urethral plate grows sufficiently with the boy to achieve a normal uroflow.
II	To evaluate psychosocial outcome in adults with hypospadias.	Cross-sectional follow-up with 167 adult men with hypospadias and 169 controls. Questionnaire including PGWB, RQ and self-constructed questions.	HrQoL was comparable to controls. We found a lower level of education and patients more often living at home with their parents. Patients with prox. hypospadias showed more differences.	Patients with hypospadias can expect a good hrQO and a normal psychosocial life with partners and children comparable to controls.
III	To describe urological outcome in adolescence for patients with proximal hypospadias.	Cross-sectional cohort study of 39/55 patients with prox. hypospadias. Evaluating uroflow, anatomic measures, sensation, penile curvature and complication rates.	Uroflows were improved but 13% still had impaired Qmax. Penile length was shorter than 90% of the population. Sensation was normal I 72%. Penile curvature was seen in 28%. 51% of patients and 82% of patients reconstructed with the Duckett procedure required reoperations.	Urological results were good for the majority, but reoperations were common. Many reoperations were performed late illustrating the need for follow-up through adolescence.
IV	To evaluate psychosocial and sexual outcomes for patients with proximal hypospadias.	Cross-sectional cohort study of 33/55 patients with prox. hypospadias compared to 31 patients with distal hypospadias and 25 age-matched controls. Questionnaire study.	Interest in sex, age at sexarche, proportion having had sex and satisfaction with sexual experiences were comparable to controls. We found no difference in PGWB, BESAA or PPS. More patients with prox. hypospadias showed uncertainty in questions regarding physical contact.	Patients with prox. hypospadias showed good psychosocial outcomes and psychosexual development but also needed considerable support. Special attention from the treating hypospadiologist in adolescence seems appropriate.

1 INTRODUCTION

Many millions of events take place when a human being is developing. Sometimes a few of these differ from the typical process and may result in an appearance different from the majority. If these differences cause problems, they may require treatment, as for many of the patients with hypospadias.



Figure 1. The miracle of life. Photo private.

Hypospadias is a malformation of the male urethra characterized by an underdevelopment of the ventral (or inferior) side of the penis with a urethral opening somewhere between the tip of the penis and the scrotum, a split prepuce and often a ventral curvature.

The surgical treatment aims to achieve a normal looking penis with the urethral opening at the top of the penis enabling forward voiding and to correct any curvature to enable sexual intercourse when growing up.

Here follows an introduction to the subject of hypospadias, with a description of the sex development, the etiology and epidemiology of hypospadias, surgical methods, outcome measures, adolescence, psychosexual development, sexual behavior and core gender identity.

1.1 SEX DEVELOPMENT

All fetuses before gestational week 7 has the same building blocks for sex development. Primitive gonads can develop into ovaries or testes, Müllerian ducts can develop into fallopian tubes, uterus and upper part of the vagina and Wolffian ducts can develop into vas deferens, seminal vesicles and the epididymis. There is a genital tubercle that will become clitoris or penis and genital swellings /ridges that becomes labia majora or scrotum.

The first operative factor in deciding the developmental route are the sex chromosomes. By fertilization, an ovum with an X-chromosome from the mother fuses with the sperm carrying either an X- or a Y-chromosome from the father. The default way is that of female development. If two X-chromosomes, the primary gonads will develop to ovaries, the fetus will develop both inner and external female genitalia and Wolffian ducts will regress. For the male development, there first needs to be a Y-chromosome containing an SRY-gene (Sex Determining Region on the Y chromosome) in order for the primary gonads to develop into testes. The testes will evolve into Sertoli cells and Leydig cells. Sertoli cells produce the Anti Müllerian Hormone (AMH), which will make the Müllerian ducts regress, provided there are receptors that answer to the AMH. The Leydig cells produce testosterone. If receptors are present, testosterone will make the Wolffian ducts develop into vas deferens, the seminal vesicles and epididymis. Testosterone is also converted to a more potent androgen, DiHydroTestosterone (DHT) by the actions of an enzyme called 5-alfareductase. DHT acts through the Androgen Receptor (AR), which is required for the development of male external genitalia.

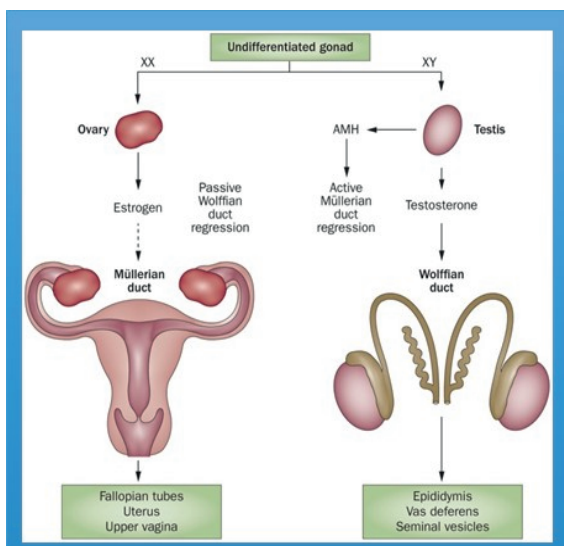


Figure 2. Illustration of differentiation of internal genitalia.

Reprinted with permission from Nature Reviews. Hutson, J. M. et al. (2014) Malformation syndromes associated with disorders of sex development. *Nat. Rev. Endocrinol.* Doi:10.1038/nrendo.2014.83

Differentiation of male external genitalia

As mentioned earlier, there is an early indifferent phase, which persists to the 3rd month of gestation for the external genitalia. In the early development the urogenital folds appear on either side of the cloacal membrane, and they fuse anteriorly at the genital tubercle. The labioscrotal folds become apparent lateral to the urogenital folds. They come together posteriorly between the urogenital and anal membranes as these separate. During the 7th week, the urogenital membrane breaks down which opens the urogenital sinus to the amniotic cavity.

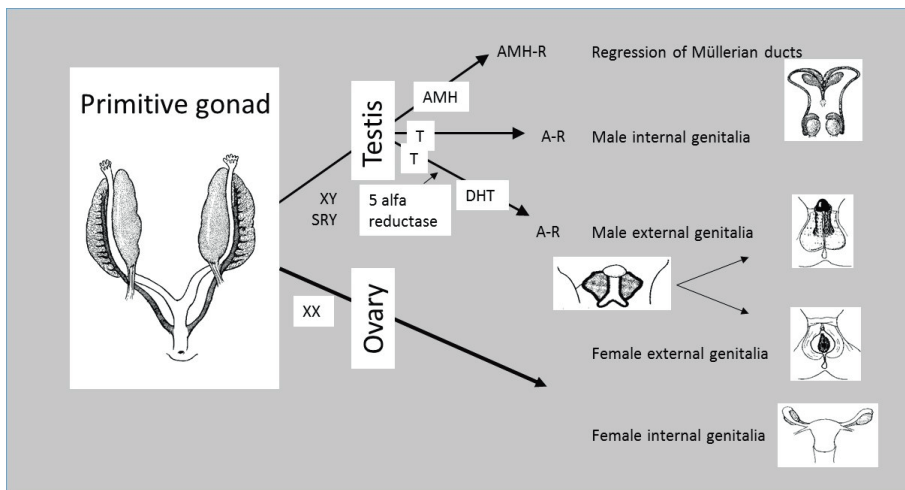


Figure 3. Illustration of determinants for developing internal and external genitalia.

Due to the effects of testosterone production from the testes, and the conversion into DHT, the genital tubercle elongates to form the penis. While doing so, the urethral groove develops on its inferior, or ventral, aspect. On its lateral side are the urethral folds and genital swellings found. The urethral groove is covered by an epithelium referred to as the urethral plate. The “Double-Zipper mechanism”(1) describes how the opening zipper leaves behind a wide urethral groove with lateral epithelial edges (urethral folds) which later fuse during the closing zipper process in a proximal to distal direction. A recent study(2) describes the series of events during the closing zipper, concluding that this gives rise to the penile urethra, the ventral corpus spongiosum and the penile raphe. This process is often completed by the end of the third trimester but the most distal part, the glanular urethra, is not completed until the end of the fourth month of gestation.

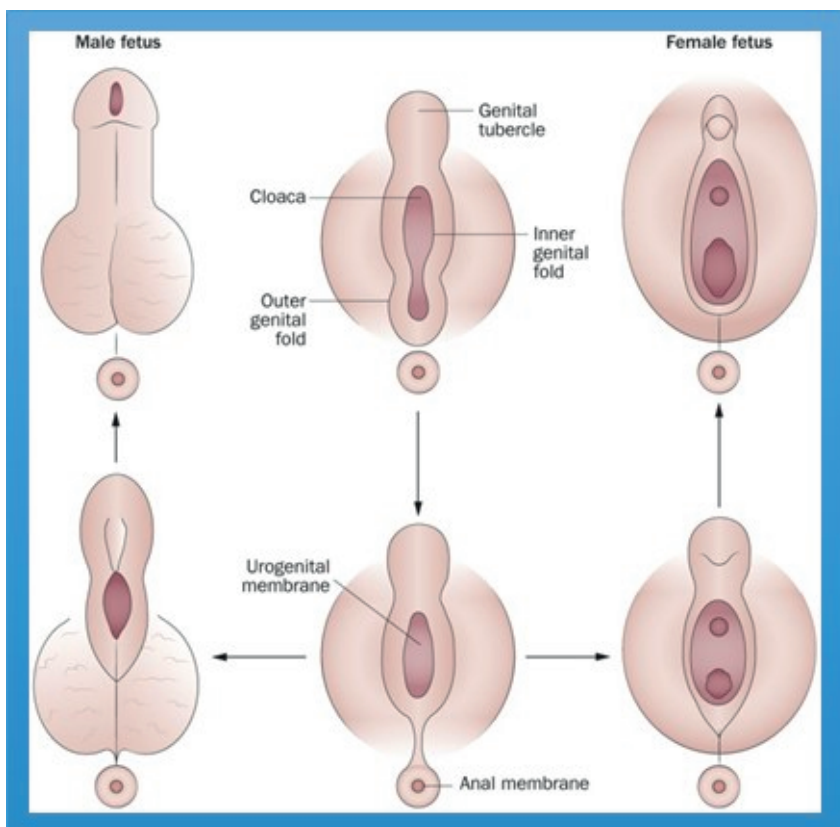


Figure 4. Development of external genitalia in male and female.
Reprinted with permission from Nature Reviews. Hutson, J. M. et al. (2014)
Malformation syndromes associated with disorders of sex development. *Nat. Rev. Endocrinol.* Doi:10.1038/nrendo.2014.83

The formation of the foreskin is dependent on a normal urethral development and follows the closure of the urethra, usually finished by gestational week 20. Preputial folds arise from the base of the glans. As it advances it grows more on the dorsal surface of the penis, then also ventrally, covering the glans and meeting and fusing in the midline raphe. The outer and inner layers of the prepuce are separated at about week 30. Remnants of the attachment between the glans and the inner layer of the prepuce can be seen as adhesions in the grown child.

A non-closure of the urethra, glans and foreskin will end up with different degrees of hypospadias.

1.2 ETIOLOGY OF HYPOSPADIAS

Many hypotheses have been proposed, including genetic predisposition, inadequate hormonal stimulation prenatally, maternal placental insufficiency factors and environmental influences. The etiology of hypospadias is now considered multifactorial(3). Despite all the research on the subject, for most individuals with hypospadias no identifiable cause is found. On a group level however, several risk factors are known.

”Maternal” factors

To be born small for gestational age (SGA) is associated with the risk of being born with hypospadias, according to several epidemiologic studies (4, 5). Furthermore, the smaller one of two monozygotic twins is the one affected with hypospadias(6). Proximal hypospadias is also more often associated with maternal hypertension, oligohydramnios and premature delivery, suggesting that placental insufficiency may play a role, possibly through insufficient hCG provision to the fetus(7). hCG acts as a growth stimulant and possibly the fetal testes will not be able to produce enough testosterone without the adequate hCG support. Furthermore, hypospadias is more common in twin or triplet births.

Hormonal and environmental aspects

Most often, hypospadias occurs isolated, but sometimes it is associated with uni – bilateral cryptorchidism and micropenis, which suggests a disturbed hormonal influence during embryogenesis (normal development described in previous section).

Some studies have suggested a potential effect of environmental endocrine-disrupting chemicals for the development of hypospadias. These are mainly animal-studies with maternal exposure to synthetic estrogens. Whether these findings are transferrable to humans is debatable(8).

Another important hypothesis is the testicular dysgenesis syndrome (TDS) that suggests cryptorchidism, hypospadias, male subfertility and testicular cancer are interlinked and due to a disturbed testicular development. The incidence of all the above have increased over the last decades, and this could be due to different degrees of expression of TDS(9). Environmental causes

are discussed, however, the pathogenesis for TDS could lie in all the etiological factors mentioned here.

Genetic factors

The idea that hypospadias has a genetic causes comes from several observations. The risk for a brother of a male with hypospadias to also be affected is between 9-17%(10). Familial aggregation can be found in about 10% of cases of isolated hypospadias. Familial clustering seems to be more common in distal and midpenile hypospadias (11, 12). Hypospadias is described as a part of over 200 syndromes, among these are Denys-Drash syndrome (undervirilization, nephrosis and the risk of Wilm's tumor (WT)), Smith-Lemli-Opitz' syndrome (malformation of the heart, lungs, kidneys, gastrointestinal tract and genitalia) and WAGR (WT, aniridia, genitourinary abnormalities and mental retardation). Mutations in specific genes that can cause hypospadias have been found in over 60 genes involved in genital development. Among the most important are the genes for the enzymes that convert cholesterol to testosterone, e.g. 17 β -Hydroxy Steroid Dehydrogenase (17 β -HSD), testosterone to DiHydroTestosterone (DHT) by 5 α -reductase (SRD5A2), the genes for the Androgen Receptor (AR) and the WT1 gene (Denys-Drash syndrome).

Disorders of sex development

DSD is a term defined as conditions in which development of chromosomal, gonadal or anatomical sex is atypical. Hypospadias can be one of the clinical findings in these conditions. There are different ways of classifying DSD. In the pathogenesis, there can be a disturbance on three levels: in the development of the gonads, in the function of the gonads or, a defect in the target organs. Clinically the phenotype can be completely female looking to any degree of male looking external genitalia, sometimes referred to as virilized female or undervirilized male. At birth, it can hence at first be difficult to determine the baby's sex.

The nomenclature from 2006 (13) shows an etiologically simplified definition of the different groups of DSD as:

- a) 46 XX DSD
- b) 46 XY DSD
- c) Sex chromosome DSD
- d) Ovotesticular DSD (sometimes described as part of (c))

The most common cause of being born with ambiguous genitalia is an enzyme defect in the adrenal glands, which, due to the inability to produce cortisone from cholesterol, instead produces high levels of testosterone. This will result in a virilization of an XX fetus (46XX DSD) and the condition is called *congenital adrenal hyperplasia (CAH)*. In a child with hypospadias and bilateral impalpable gonads *CAH* must be ruled out as it could be life-threatening due to the lack of cortisone and aldosterone.

In 46 XY DSD, the most commonly occurring diagnosis is Partial Androgen Insensitivity Syndrome (*PAIS*), which consists of a defect in the function of the AR resulting in an undervirilization with varying degree of hypospadias. In the case of CAIS (Complete Androgen Insensitivity Syndrome), testicles develop that produce testosterone, but none of the target organs can respond, resulting instead in a complete female external genitalia and mental development.

Defects in the synthesis of testosterone are seen in a *deficiency of 17 β -hydroxylase (17 β HSD)* and *5- α -reductase deficiency*. When 17 β HSD is missing, androstenedione is not converted to testosterone. In puberty however, the testes produce testosterone to levels between 10-fold and 100-fold those of a newborn child, which is sufficient for genitalia to virilize. *5- α -reductase* is the enzyme responsible for converting testosterone to the more potent DHT. A lack of this enzyme can be total or partial and will result in genital phenotypes varying from completely female looking to a small phallus with hypospadias. Both genital and psychological virilization can occur in puberty due to an isoenzyme in liver and skin that converts testosterone to DHT.

Hypospadias can also be present in *sex chromosome DSD with mosaicism X0/XY*, also called *mixed gonadal dysgenesis*. In *mixed gonadal dysgenesis* you often find a dysgenetic gonad on one side and a more or less cryptorchid testicle on the other. In *ovotesticular DSD* you will find both ovarian and testicular in the same individual, even in the same gonad. The degree of virilization depends on the amount of functional testes producing testosterone. To be born with ambiguous genitalia is uncommon.

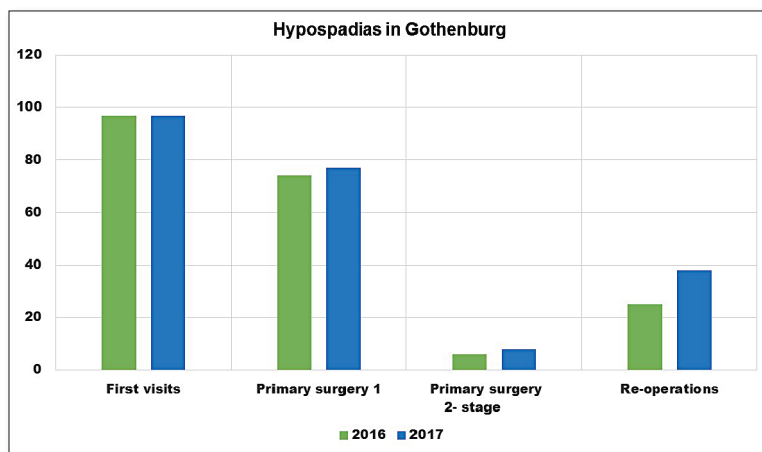
In Sweden, only 10-15 children per year or 1/10 000 are born with ambiguous genitalia.

1.3 EPIDEMIOLOGY

The prevalence (the total number of cases in a population at a given time) of hypospadias, measured at the time of birth, varies between countries. Increases and decreases over time are described. Many studies have been conducted but factors affecting results such as improved reporting and increased awareness of hypospadias are difficult to rule out. A recent report published the prevalence in Europe from 23 EUROCAT registers between 2001-2010 for almost 6 million births. They describe an overall stable prevalence of 1/538 in Europe (14). The prevalence has been reported to be the highest in North America (1/290) and the lowest in Asia (between 1/16700-1/1450). Although almost 90 million births were covered in this literature review investigating prevalence of hypospadias in the world, the true prevalence was difficult to estimate, due to many methodological factors(15)

A register-based epidemiological study from Sweden showed the prevalence to be 1/125 born male infants in 2009(4). An increase from 1/223 to 1/125 between 1990-2009 was shown, and this was not explained by an increase in known risk factors, such as twin births, SGA, increased use of IVF, increased immigration or higher incidence of maternal obesity. The increase included both distal and proximal cases. Proposed explanations have been an effect of improved surgical techniques with improved fertility as a consequence, or possibly the effect of increased influence of environmental endocrine-disrupting chemicals, but to date, there are no hard data to support this.

Table 1. Number of patients with hypospadias treated in Gothenburg 2016-2017 from the local register. The number ought to be approximately 1/4 of the patients in Sweden. 100 000 children are born every year, approximately 50 000 boys, yielding 400 new cases according to 1/125.



1.4 CHARACTERISTICS OF HYPOSPADIAS

Anatomy

The characteristics of a hypospadiac penis are threefold. A urethral opening located between the glans and the base of the penis, a ventral curvature and a hooded foreskin with excess of skin on the dorsal side and a lack of skin on the ventral side.

Anatomically, the anomaly can be described as follows: the glans opens ventrally. One segment of the urethral tube is missing and instead a urethral plate is seen from the place of the urethral opening to the glans, between the two corpora cavernosa. The most distal part of the *tubular* urethra (varying length) is hypoplastic and not surrounded by any corpus spongiosum, and often covered by a thin layer of skin tightly stuck to it. The division of the corpus spongiosum is always proximal to the ectopic meatus and the divided corpus spongiosum extends laterally up to the glans, which can often be seen as a small cutaneous ridge. The frenular artery is always missing. Proximal to the division of the corpus spongiosum all the structures forming the ventral aspect of the penis are normal. The division of the corpus spongiosum is hence the proximal demarcation of the malformation. The dorsal aspects of the penis are normal(16).

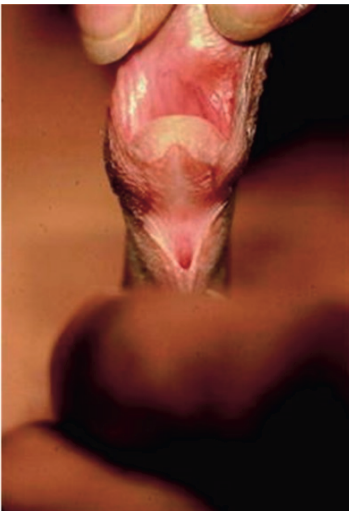


Figure 5. Picture of a midpenile hypospadias.

With permission from Zaontz M.R. (2010)
*Disorders of Male External Genitalia:
 Hypospadias, Epispadias, Concealed Penis, and
 Urethral Disorders.* In: Godbole P., Koyle M.,
 Wilcox D. (eds) *Guide to Pediatric Urology and
 Surgery in Clinical Practice.* Springer, London

The anatomy regarding angiology and neurology is of importance for hypospadias surgery. The pudental arteries give rise to the deep arteries in the middle of the corpora cavernosa, and to the dorsal arteries, which provide blood supply to the glans and prepuce. The latter run just lateral to the midline on the dorsal side, under the deep fascia (Buck's fascia). Branches run along the outer sheet of the prepuce and then turn 180° to follow the inner preputial sheet and drain in veins at the level of the coronal sulcus. The nerve bundle runs just lateral to the dorsal artery on both sides underneath Buck's fascia.

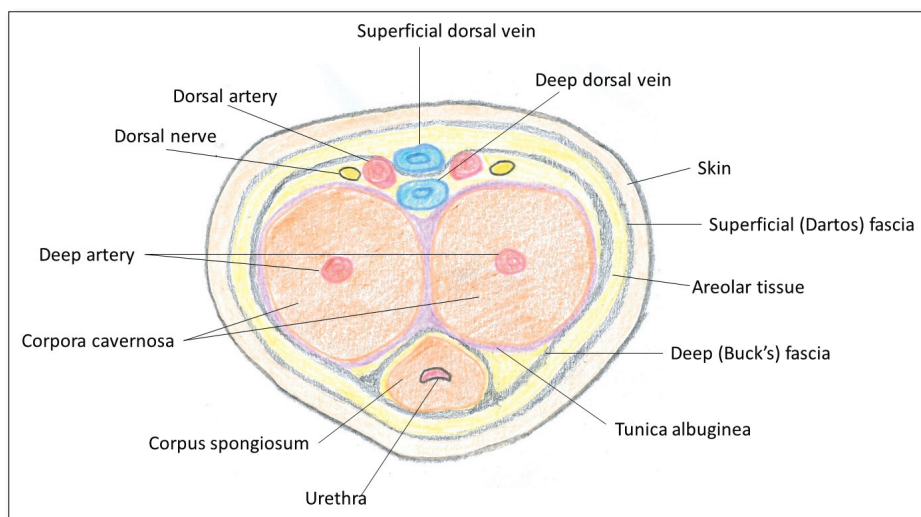


Figure 6. Illustration of the penile anatomy, cross-section.

There are some rare variants of hypospadias, e.g. the so called 'hypospadias sine hypospadias' and the 'megameatus intact prepuce'. The first is characterized by a ventral curvature, but a normal situated meatus and a distorted foreskin. The second has a normal, circular foreskin and a meatus at the sulcus coronarius, which opens up to a wide fossa navicularis on a non-closed glans(3).

Severity

The severity or phenotype of the hypospadias is often described by the location of the ectopic meatus. As described in the precious section, a more correct definition is the division of the corpus spongiosum. This is preferably

determined at the time of surgery after degloving of the penis. The meatus may then present much more proximally than before.

Historically the terms anterior and posterior, as well as mild and severe hypospadias have been used. Most pediatric urologists presently agree to henceforward classify hypospadias according to the division of the corpus spongiosum or the location of the meatus after degloving, as distal, midpenile (sometimes considered part of distal) or proximal. More proximal hypospadias usually also associated with more penile curvature. Within the different groups, certain subgroups may be found, as shown in Figure 7.

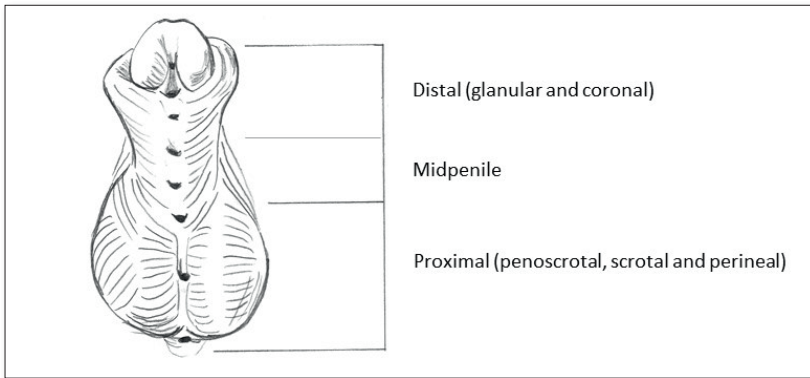


Figure 7. Different degrees of hypospadias, i.e. phenotypes.

The term “hypospadias cripple” is sometimes used as separate group. It refers to patients with pronounced scar tissue due to numerous re-operations and complications. This group presents great challenges and only very experienced surgeons should consider performing further reconstructions with the aim to improve outcome. However, hypospadias cripples can result from all the different phenotypes of hypospadias.

1.5 SURGICAL MANAGEMENT

Initial management

When assessing a child born with hypospadias, the first important thing to notice is whether urine passes easily or not. Especially in distal cases, a stenosis can be present at the ectopic meatus that might need to be addressed before the reconstructive surgery is planned. Next, is to examine for other signs of undervirilization, such as uni- or bilateral cryptorchidism, micropenis or abnormal scrotum, in which case the child should be referred to a DSD-team without further delay for genetical and hormonal screening. If no such signs, the parents should be informed about hypospadias, and told not to perform a circumcision before consulting a pediatric urologist since the prepuce sometimes is required for reconstruction. The first pediatric urologist consultation normally takes place at approximately 3 months of age at our clinic.

For most hypospadias patients no further medical investigation is required. Although hypospadias is most commonly an isolated malformation, there are sometimes associated anomalies of the urinary tract, especially in proximal hypospadias, while the incidence in distal hypospadias is the same as in the normal population (17). The most commonly found associated anomalies are inguinal hernia, undescendent testes, PUJ-obstruction (Pelvo Ureteral Junction), renal agenesis, Vesico Urethral Reflux (VUR), persistent Müllerian structures and DSD-conditions. For patients with proximal hypospadias an endoscopic evaluation of the urethra is often carried out to detect any remnants of Müllerian ducts that can cause problems to catheterize the urethra, urinary obstruction or urinary tract infections (UTIs) after reconstruction. A Müllerian remnant in form of a “vagina masculinum” (utricle cyst or dilated utricle) is present in 11-14% of all hypospadias and in up to 50 % of patients with perineal hypospadias(18).

Timing of surgery

The current European guidelines recommend surgery to be performed between 6-18 months of age (19). These recommendations are based on the earlier findings in some studies of a higher complication rate for patients after reconstruction at an older age(20, 21), and the risk of a more negative body

image and a diminished satisfaction with overall body appearance for those having had surgery at an age when they remember it (22). Genital awareness is known to begin at 18 months of age (17) why performing the surgery before then is considered preferable, and the risks of general anesthesia after the age of 6 months is considered no greater than when older, if performed in a clinic with experience of pediatric anesthesia.

Recent strong voices have however been raised, in particular from support groups of DSD, to postpone surgery until the child is able to give informed consent. Some of the groups with DSD-diagnoses, but not all, have shown a higher risk of gender dysphoria when growing up (CAH girls) and a higher frequency of requiring sex change (17 β HSD, 5 α -reductase deficiency, as well as children with genital malformation who grew up as girls but had a normal level of male hormones at birth, requesting a change from girl to boy, e.g. cloacal exstrophy)(23). There are also studies that present results with no gender dysphoria found in boys and men with DSD and atypically low androgen effects, i.e., boys and men with partial androgen insensitivity syndrome or mixed gonadal dysgenesis(24, 25). Until the 1980s, almost all XY-DSD individuals with severe under-virilization (of androgen synthesis, PAIS, and mixed gonadal dysgenesis) were assigned to the female sex. In one study on 46XY-children born with ambiguous genitalia, gender dysphoria was reported in 23 % (9/39) independent of the sex they were raised in (5 men, 4 women)(26). This study did unfortunately not reveal the underlying DSD-diagnoses for these individuals. Indeed, assigning a sex for rearing in children with ambiguous genitalia is a delicate matter. Findings like these could advocate postponing irreversible (feminizing) genital surgery until the child is old enough to be deciding for itself.

The European Council has recently presented a resolution (27) that makes performing genital surgery before the patient is able to give informed consent highly questionable. The Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment, Juan E. Méndez, presented a report (28) to the General Assembly of the UN, Human Rights Council in 2013 stating that “These procedures [genital-normalizing surgeries] are rarely medically necessary, can cause scarring, loss of sexual sensation, pain, incontinence and lifelong depression and have also been criticized as being unscientific, potentially harmful and contributing to stigma.” Most pediatric urologists interpret this as being aimed specifically at the other DSD-diagnoses and not hypospadias per se, but the debate is ongoing(3, 22).

Surgical methods

The condition of hypospadias has been described and a surgical treatment proposed as early as in the second century by Galen, a personal physician of many roman emperors. He described a type of stretching and redistribution of skin from the dorsal to the ventral side in distal hypospadias(29). Since then, over 200 different surgical techniques have been described. They can be divided into three eras:

- 1) Stretching during the early period
- 2) Tunneling during the Middle Ages and
- 3) Flaps during the modern period

The changes in these periods were closely related to advances in new surgical instruments, anesthesia and newer suture materials.

The aim of surgical reconstruction is to achieve a straight penis to enable sexual intercourse, a meatus enabling forward voiding without problems and a satisfactory cosmetic result.

Here follows a description of the most commonly used techniques during the time of study I-IV in our institution.

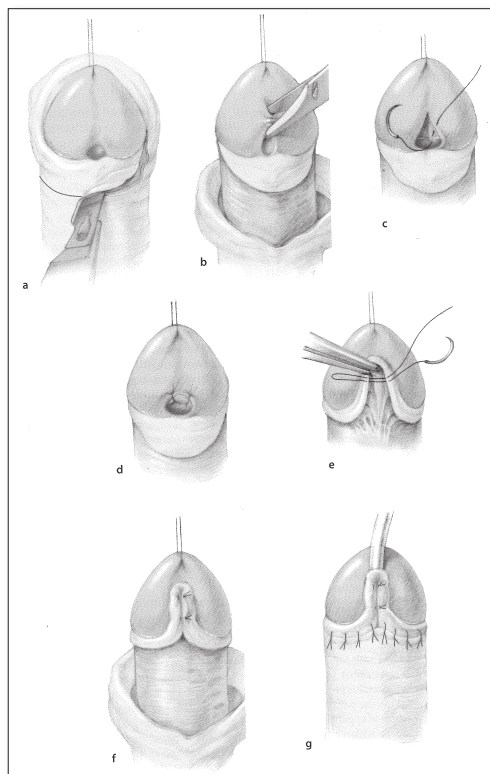


Figure 8. Illustration of the MAGPI procedure with circumferential subcoronal incision, excision of bridge of tissue between meatus and glanular groove. Two-layer closure of the glans edges reconfigures a conical meatus.

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The MAGPI procedure (Meatal Advancement and Glanuloplasty procedure) is used in patients with distal hypospadias, more precisely with glanular hypospadias. It does not involve an actual urethroplasty but merely a remodeling of the glans. A preputioplasty or circumcision is performed concomitantly.

The TIP procedure (Tubularized Incised Plate urethroplasty) was first described by Dr. Warren Snodgrass in 1994, initially intended for distal hypospadias (coronal to distal penile), but successively used for more proximal cases (midpenile to penoscrotal) as well. With this technique, the urethral plate is used to create a neourethra by mobilizing the edges and tubularizing the plate over a catheter after making an incision in the midline, dorsally of the plate to enhance the diameter of the neourethra, Figure 9. A preputioplasty or a circumcision is performed concomitantly.

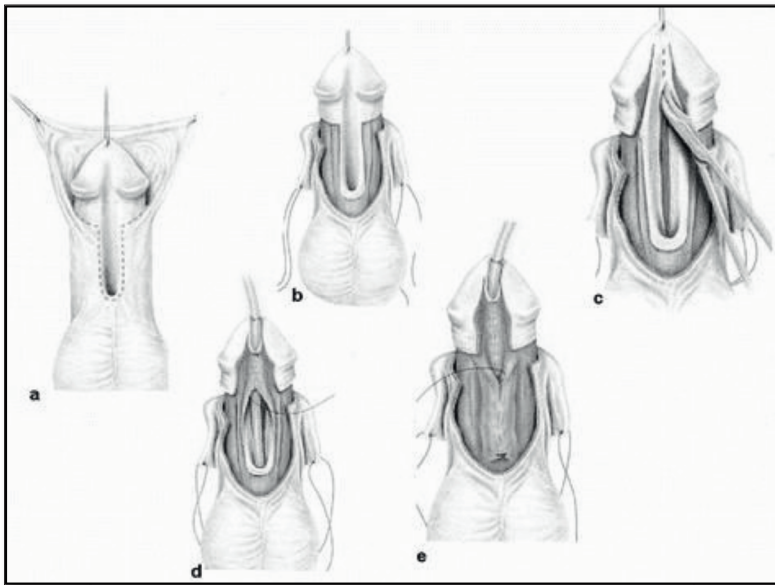


Figure 9. Illustration of the TIP procedure (Tubularized Incised Plate urethroplasty) for proximal hypospadias. a, b: Skin incision preserves urethral plate. c: Midline incision of urethral plate. d: Tubularization of urethral plate. e: Spongioplasty approximates corpus spongiosum over neourethra before a dartos or tunica vaginalis barrier flap is added

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The Onlay procedure was used in patients with midpenile to proximal hypospadias before the TIP procedure was introduced. With this technique the urethral plate is also utilized but as a “floor” with a covering “roof” of a pedicled prepuce flap with its vascular supply intact. Because this technique requires two suture lines in the neourethra, the risk for fistulas is great. Figure 10. This procedure requires circumcision.

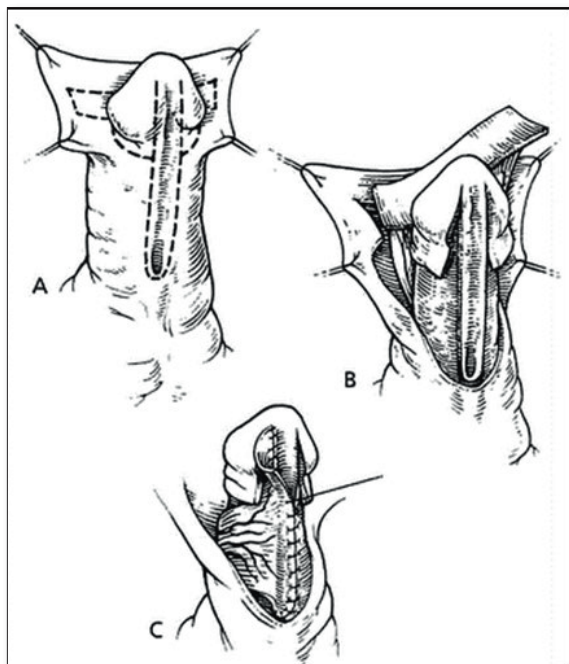


Figure 10. Illustration of the Onlay preputial flap procedure. **a, b:** A rectangular flap of appropriate length and a width of approximately 8–10 mm is cut from the inner prepuce, maintaining its blood supply. **c:** The flap is rotated ventrally and sutured to the urethral plate. The pedicle of the flap is used to cover the neourethral suture lines.

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The Duckett procedure was used in the most proximal hypospadias with the most severe curvature and the worst quality urethral plate. With this technique the urethral plate is divided. When the urethral plate is divided, the penis is often straightened and the distance from the meatus to the tip of the glans is left with a section that requires a substitute urethra. The inner layer of the prepuce is prepared in the same manner as with the Onlay procedure with great care taken to preserve the blood supply, and thereafter the flap is turned to the ventral side, tubularized over a catheter and sutured in place. This procedure also requires circumcision.

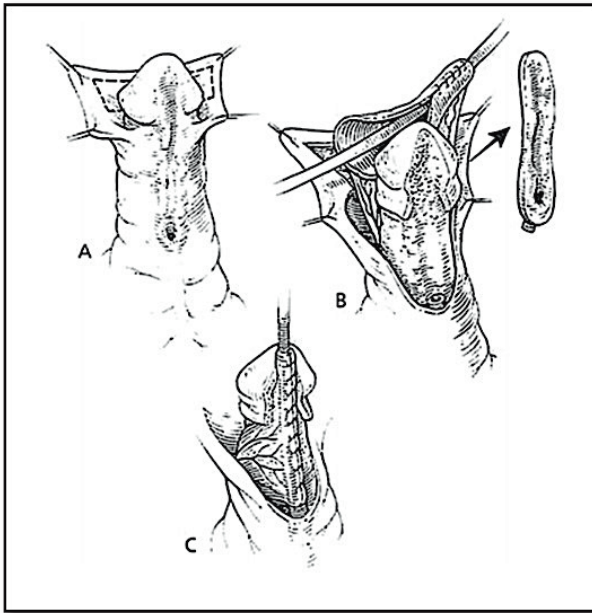


Figure 11. Illustration of the Duckett procedure (tubularized preputial flap). **a:** A rectangular flap of appropriate length approximately 14 mm wide can be harvested from the inner prepuce. **b:** Following resection of the urethral plate, the flap is mobilized and then tubularized over a stent. **c:** The neourethra is rotated ventrally, placing the suture line against the corpora cavernosa.

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In all of the techniques mentioned above, an evaluation of penile curvature is part of the procedure. Often the evaluation includes an artificial erection test intraoperatively. When penile curvature is not completely reversed after degloving of the penis and excising all hypoplastic tissue (chordee), an additional decurvature procedure can be performed along with the urethroplasty. Different methods are available.

If the curvature is mild, a dorsal plication is often sufficient. This can be performed as a **Nesbit procedure** where parallel incisions are made superficially into the tunica albuginea of the corpora cavernosa adjacent to the neurovascular bundles at the point of the greatest curvature. 6-0 prolene sutures are placed burying the knot. After Baskin and colleagues in their studies found no sensory nerves at the 12 o'clock position(30), the **Baskin procedure** instead performs the plication in the midline. When the curvature is greater than 30 degrees, a plication is rarely sufficient, but instead the urethral plate might need to be transected (as described for the Duckett procedure). Before deciding to do so, some recommend to first **mobilize the plate** from the meatus to the corona, which might release curvature enough to allow straightening with a plication(31). A transection of the urethral plate may result in a complete straightening, or may be combined with a dorsal plication. Another decurvature procedure is **rotation of the corpora** where the

dissection is performed ventrally into the intercorporeal septum to separate the corpora cavernosa and then rotate them laterally to straighten the penis.

Complications

Complications are common after hypospadias surgery. The tissues are hypoplastic with impaired healing conditions. Infection, hematoma or edema can disturb healing further. Some techniques depend on flaps that may have a lot of strain on its vascularization. Examples of complications are: preputial dehiscence, glans dehiscence, fistulas, stenosis or strictures, diverticula formation with sacculation and dilatation of the urethra and recurrent curvature. Defect wound healing may also lead to pronounced scarring and a less satisfactory cosmetic result. Unsatisfactory cosmetic results have been common, but hopefully, more satisfactory results will follow with new techniques. Dissatisfaction may, in addition to previously mentioned complications, also be due to irregular suture lines, skin blobs, redundant skin or merely unsatisfactory penile size.

The complications that occur are of varying severity and are treated in different ways. Strictures or stenosis may sometimes be treated with dilatations or internal uretrotomies, but can also require more extensive surgical interventions. Preputial dehiscences or preputial fistulas may result in a redo preputioplasty or a circumcision and glanuloplasty, alternatively left without any intervention if the patient is not interested in further surgery. Urethral fistulas, diverticulas or sacculations are corrected surgically, as well as recurrent penile curvature if associated with subjective inconvenience for the patient.

Follow-up

Most studies conclude that follow-up should be continued until after puberty. However, in reality few hypospadias centers actively follow their patients, but leave it up to the parents or adolescents to request a review appointment if problems occur. In our clinical praxis, all patients having had a urethroplasty will have a postoperative follow-up after 3 months, at five years and 15 years of age at the minimum. The last two include uroflowmetry. If problems are anticipated that cannot be addressed before the patient leaves pediatric care he will be transferred through an adolescent appointment conducted with both a pediatric urologist and an adult urologist for further follow-up.

1.6 OUTCOME MEASUREMENTS

Evaluation of the result of a treatment has different aspects. Historically, mortality and morbidity have been the main outcome measures. They remain important cornerstones in evaluating the success of a treatment. In pediatric surgery, however, mortality is fortunately rare. Patient reported outcome (PRO) have become more common during the last decades. PRO aims at evaluating how well the treatment has met the expectations of the patient, not necessarily the same as those of the physician. Instruments to properly measure this are being developed in collaboration between experts, physicians and patients, but to our knowledge there is no such specific PRO instrument for hypospadias so far. In this thesis, we aimed at evaluating not only the evident visible results of surgery, but also patient satisfaction and if other aspects such as body esteem and general well-being might be affected.

Urinary function

One of the most important outcomes is a satisfactory urinary function. In some studies this is evaluated simply by asking the patient if they experience any problem with voiding. This is however not uncomplicated, since, as for most congenital conditions, the person affected has nothing to compare with. If it has always taken more than a minute to empty the bladder, this may not be considered a problem. To objectify urinary function, *uroflowmetry* and *ultrasound to check for pathological PVR* can be performed. The boy is asked to void on a special toilet where voided volume and voiding time is recorded, resulting in a maximum flow rate (Qmax) and a diagram with a curve expressing voided volume on the Y-axis and voiding time on the X-axis. Patients with hypospadias have been shown to have an obstructive flow pattern after surgery, but also before surgery (32), perhaps due to the lack of supporting spongiosa and after surgery due to a non-elastic hypoplastic urethra(33). Also in adults with hypospadias, urinary flow has been shown to be lower than in controls(34, 35).

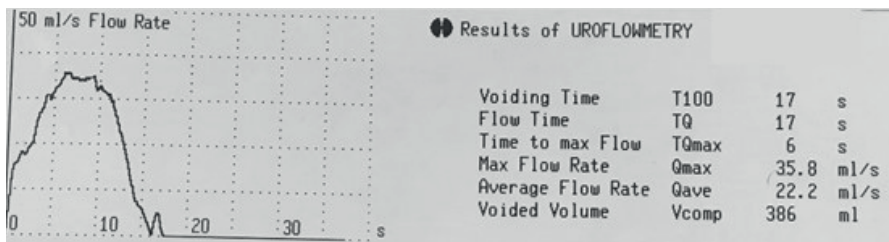


Figure 12. Example of a uroflowmetry result with a bell-shaped (normal) curve.

Additional ways of objectifying urinary function includes asking specified questions directed at finding out symptoms of expected problems. For instance, a person who finds it normal to spend over a minute voiding might still affirm straining to be able to void, which could indicate a urethral stricture. There are also structured questionnaires for LUTS, which can be used. These mainly focus on problems due to an enlarged prostate and will miss symptoms specific to hypospadias, e.g. fistulas or diverticulas causing a double stream or dripping.

Cosmetic appearance

The aim of surgical reconstruction is to achieve an acceptable cosmetic outcome. The definition of “acceptable” is however, not clear. A surgeon might assess results as acceptable where patients and parents will not. Studies have also shown that there is a difference between patients evaluation of the cosmetic result and a surgeons evaluation(36), where patients were less satisfied than the surgeons. Many studies have shown that patients with hypospadias are not completely satisfied with results, especially not patients with proximal hypospadias (37-39) who are mainly dissatisfied with length, curvature and sometimes with being circumcised. In an attempt to objectify the cosmetic outcome a standardized scoring system, the Hypospadias Objective Scoring Evaluation (*HOSE*) was designed (40). It evaluates the meatal shape and position, urinary stream, straightness upon erection and the presence and complexity of any fistulas. It has shown good inter-rater reliability between surgeon and nurse as well as between surgeon and parent (40). The score range between 5-16 points and a score of ≥ 14 points have been considered an acceptable outcome. A drawback with this instrument is that it was not developed in collaboration with patients with hypospadias and it does not include any item inquiring about patient satisfaction.

The instrument Pediatric Penile Perception Score (*PPPS*)(41) and Penile Perception Score (*PPS*)(42) are identical but validated for different age-groups. They inquire about patient satisfaction with the shape and position of the meatus, shape of glans, shape of penile skin and general appearance. Answers range from very dissatisfied to very satisfied and are scored from 0-3 on each item. Total score range from 0-12 points. This instrument is likewise not developed together with patients with hypospadias but provides information on the patient’s satisfaction with results. When developing *PPPS* and *PPS*, a question on satisfaction with penile axis (curvature) was removed because of conflicting results between patients and controls and due to poor intercorrelation with general appearance. The question on satisfaction with

penile size was removed since this is not a factor that is amenable to hypospadias repair. These are nevertheless factors that seem very important to patients operated for hypospadias, and still deserve to be evaluated.

Body Esteem

Body image and body identity formation is particularly important during adolescence as a result of psychological, social, and biological changes. One part of body image is body esteem, which contains several aspects, described by Mendelsson et al (43) as (1) people's overall evaluations of their appearance, (2) their evaluations of their weight, and (3) their views about what other people think about their own looks. These aspects can be evaluated with the Body Esteem Scale for Adolescents and Adults (BESAA). Other aspects also influence the body image, such as the body ideals presented to us by media, social influences and processes of objectification of our body(44). If body esteem is impaired, one might expect that penile perception could be affected as a consequence of this rather than as a consequence of surgical results. The opposite could also be true; a negative penile perception could influence body esteem.

There are studies that have previously investigated Body Esteem in patients treated for hypospadias. Örtqvist et al found no difference between patients and controls(39). Vandendriessche found a better evaluation of physical appearance and body perception in 10 hypospadias patients compared with controls(45). Kiss studied proximal hypospadias and included one question on body esteem and found no difference compared with controls(38). The BESAA instrument evaluates body esteem and the instrument consists of 23 statements, with answers ranging from never to always, scored 0-4 points, and negative items reversely scored.

Quality of Life (QoL)

QoL is a term created by American political economists in the 1950s.

'The important goal is not about the quantity of our possessions but about the quality of our lives'
~John Kenneth Gailbraith, 1958. (The Affluent Society)

Quantitative measures of societies (BNP/capita, number of millionaires, number of cars, mobile phones, computers, living area, money spent on health care, etc.) explain surprisingly little about how satisfied people are with their lives.

There are three groups of psychological/philosophical theories with different views upon what QoL is. a) The hedonistic theory – emphasizing emotional experiences of wellbeing, happiness and pleasure. The happier you are, the better the quality of life is. b) The wish fulfillment theory – personal wishes and needs are satisfied. The more you obtain what you want, the better the quality of life is. And the opposite – The more you are able to avoid circumstances that you do not want, the better the quality of life is. c) The theories about important objective conditions – emphasizing universal facts and circumstances that are important for all humans (e.g. constructive, engaging and productive activities, positive social relations, satisfying aesthetic experiences (music, art, environments, clothes), contact with reality, acceptable physical and psychological conditions, opportunity for personal development and growth, freedom and autonomy) The more you have of these circumstances, the better the quality of life is. Another question is “To what extent does happiness depend on external events and circumstances (bottom-up) - or how we perceive ourselves and life (top-down)”.

Health related Quality of Life (hrQoL)

HrQoL is more commonly used in reporting outcome after treatment. It is still a very wide concept and overall QoL-state might influence the ratings of hrQoL. The World Health Organization (WHO) defines health as: “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”.

It is rare that the health care drastically change people’s outlook on life, but more often changes symptoms, functioning and general wellbeing.

HrQoL is defined as personal, subjective experiences of:

- Physical functioning
- Mental functioning
- Role functioning (work, family, leisure)
- Symptoms
- General health/wellbeing

When evaluating hrQoL, three different types of instruments can be used. General instruments, domain specific or diagnose specific instruments.

General instruments consist of items general and relevant for all populations, young/old and ill/healthy. For investigating health status in general populations (public health research) general instruments should be used. Also when investigating the 'subjective burden' of a certain condition due to e.g. age, illness or injury, a general instrument is recommended to enable relevant comparisons with other reference groups. If information only about a certain type of health perceptions, for example mental health or sleep disturbances is investigated, a domain specific instrument could also be used. In comparisons between different types of treatment/caring/rehabilitation – clinical trials - a diagnosis-specific instrument is recommended. These types of instruments give specific information about symptoms/treatments effects that are typical for a specific condition and its treatment.

Psychosocial outcome

One way to describe the outcome or try to evaluate a possible effect of a treatment or disease is to describe psychosocial outcome. This should include the social status of the individual, his functional capacities in society and an evaluation of mental health.

Previous studies have shown that patients with hypospadias are more hesitant in seeking romantic contact compared with controls (37, 46, 47). This could be due to intimidation or insecurity regarding penile appearance or possibly an effect of being teased or bullied at school due to a different penile appearance. An impaired self-esteem could impact the capability for social interactions such as daring to approach people to create relationships and to participate in leisure activities, e.g. those including changing clothes in locker rooms. A study by Berg et al (48) showed, in 1981, that adult patients with hypospadias were shy and had been teased more as children. Sandberg et al (49) described in 1989 behavior difficulties and poorer school performances in children with hypospadias.

Bullying, as well as repeated absence from school due to hospital visits, could result in an impaired performance at school. Berg et al(48) described lower qualified professions in their cohort of patients with hypospadias but subsequent studies have shown comparable educational levels (49-51).

Psychiatric comorbidity has not been studied in depth in hypospadias. Berg et al and Sandberg et al found an increased frequency of anxiety, signs of depression and less externalizing behavior in men with hypospadias in the

1980s. Butwicka et al found, in a register study of over 9000 patients with hypospadias and their brothers in comparison with controls, an increased risk for intellectual disability, autism spectrum disorders, ADHD (1.5; 1.3-1.9), and behavioral/emotional disorders compared with controls as well as an increased risk for ASD in their brothers. The associations remained significant also when controlling for socio-demographical, perinatal, and somatic factors (52). Örtqvist et al found no increase in psychiatric symptoms compared with controls (53).

Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) is a term coined by professor Gillberg(54), referring to children presenting in clinical settings with impairing child symptoms before age 3 (–5) years in the fields of (a) general development, (b) communication and language, (c) social inter-relatedness, (d) motor coordination, (e) attention, (f) activity, (g) behavior, (h) mood, and/or (i) sleep. The syndromes encompassed under the ESSENCE umbrella acronym are: Autism Spectrum Disorders (ASD), Attention Deficit and Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), Speech Language Impairment (SLI), Learning Disability (LD), Nonverbal Learning Disability (NVLD), Tics/Tourette Syndrome, Bipolar Disorder, Behavior phenotype syndromes, Rare Epilepsy Syndromes and Reactive attachment disorder. Approximately 10% of school children in Sweden (13% of boys and 7% of girls) can be diagnosed with problems related to ESSENCE (54). The problems often continue up through adult life, even if approximately 50% no longer have all the criteria for a diagnosis. A not neglectable proportion of them will carry disability pension, unemployment allowance or social welfare allowance from a young age(55). This is of interest from the perspective that Nordenvall et al found an unexplained increased risk of receiving disability pension among patients with hypospadias in a recent Swedish register-based study(56), even after stratifying for comorbidities such as low birth weight, prematurity, associated malformations and psychiatric illness.

Psychological well-being

Psychological well-being is one aspect of hrQoL. At the most basic level, psychological well-being is quite similar to other terms that refer to positive mental states, such as happiness or satisfaction, but of course, many aspects affect the psychological well-being. The authors of a text book on Gender Dysphoria and Disorders of Sex Development(23) suggest

considering experience with sexuality, the impact of hormonal dysregulation, body image, surgery, and psychological trauma on mental well-being as well as social relationships, both as end points and as determinants of psychological well-being. All of these aspects are not available in one instrument for evaluation; however, the evaluation conducted in this thesis encompasses several of them.

The *Psychological General Well-being (PGWB)* instrument is a general instrument designed to reflect the subjective state of mind during the previous week(57). It evaluates six dimensions: anxiety, depressed mood, positive well-being, self-control, general health and vitality. The 22 items are scored 0-5 and a higher score represents a better outcome.

Sexual function

The definition of health by the WHO includes a satisfactory sexual life. Many aspects are involved in making sexual life satisfactory, but one is having a good sexual function. Hypospadias, with or without complications after surgery, may be associated with difficulties such as an impaired sensation, impaired ejaculatory function or recurrent curvature making erection painful and intercourse troublesome. Early studies have shown a higher degree of anejaculation and erectile difficulties in adults with proximal hypospadias (37, 58-60). Describing sexual function as an outcome after hypospadias surgery is of utmost importance, however the time lapse between surgery and sexual maturity sometimes constitutes an obstacle. By consistently reporting sexual function as an outcome, hopefully hypospadias care, and consequently outcome, can improve further.

Many different instruments for evaluating sexual function have been developed in the course of the pharmaceutical interest of treating sexual dysfunction. In most of these, the different phases of the sexual response cycle are evaluated (desire, arousal, orgasm and resolution). One of the more commonly used instruments is *Derogatis Interview for Sexual Functioning – Self Report (DISF-SR)*. It consists of 26 items evaluating the domains Sexual Cognition/Fantasy, Sexual Arousal, Sexual Behavior/Experience, Orgasm and Sexual Drive/Relationship.

Psychosexual development

The psychosexual development refers to “the process by which an individual becomes more mature in his sexual feelings and behavior. Gender identity, gender role behavior, and sexual orientation are the three major areas of development.”(61). For this to function well many different parts need to be present, for example social competence may influence development of friendships, which is important for romantic functioning(62). Before Freud, “sexologists” tended to think that sexual capacities appeared suddenly at the onset of adolescence. With psychoanalysis, the view shifted to claiming libido as an element present from birth. However, even if some level of exploring occurs in childhood, adolescent sexual development really represents the beginning of adult sexuality(63).

When evaluating psychosexual development, one aspect is evaluating if developmental milestones are reached similarly as in peers. However, it is important to note that achieving developmental milestones is not equivalent to satisfaction with sexual/romantic activities. There are few studies on psychosexual development in adolescents with hypospadias, and those have shown divergent results probably somewhat depending on how questions are asked. Two studies found no difference in the age of reaching sexual milestones (46, 64). One study found fewer patients with hypospadias having had sex compared with controls (65). Most studies are not differentiating between phenotypes, and clinical outcomes are seldom described in the cohort of patients answering questionnaires.

Sexual orientation / Gender identity

This thesis has no intention of trying to explain the grounds for different sexualities or gender identities. It will most briefly inquire about these aspects in paper IV, so therefore a short introduction will follow.

Prenatal exposure of androgens is thought to effect higher brain functions during fetal life in the developing brain(66). Girls born with CAH have shown masculinized gender role behavior as children(67). The recalled childhood behavior correlates with adult gender role behavior such as sexual orientation, choice of profession and leisure activities(68). Regarding determinants for gender identity, much less is known. Prenatal androgen exposure has not been shown to correlate to a convincing degree to gender identity(69, 70). The degree of prenatal androgen exposure (measured as the

degree of virilized genitalia) was not associated to the degree of masculinized gender identity (71, 72).

Gender is an essential part of human identity. Since one's gender assignment ordinarily is solid and many features of life—including recreational, academic, occupational, and relationship activities—are affected by gender, it seems likely that most people give some time to reflect on questions like: How well do I fit with my gender category? Likely this begins in childhood(66) and, during the changes in adolescence these reflections may become more prominent.

Girls born with Congenital Adrenal Hyperplasia (CAH) have an excessive testosterone level during fetal life. Hypospadias is thought to develop due to a deficiency of effects of androgen during early fetal development. These circumstances could imply that patients with hypospadias might have an atypical gender role behavior and core gender identity in a similar manner as girls with CAH. However, genital development occurs during the first two months of pregnancy and sexual differentiation of the brain starts in the second part of pregnancy, hence these processes may be influenced independently of each other(72). Also, there are certainly many other aspects that play important roles in this development.

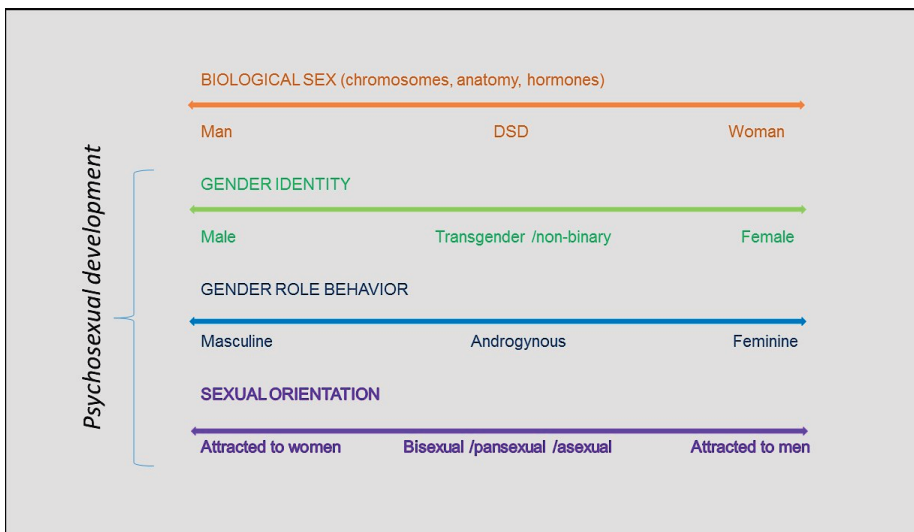


Figure 13. Illustration of different aspect of sexual development.

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In 1948, Dr. Alfred Kinsey, Wardall Pomeroy and Clyde Martin interviewed thousands of persons and concluded that sexual behavior; thoughts and feelings towards the same or opposite sex were not always consistent across time. They developed the Heterosexual-Homosexual Rating Scale, often referred to as the *Kinsey scale*. In study IV, we included questions where participants rated how same-sex- or opposite-sex-oriented their behavior and fantasy had been during the last month and during their lives according to a five-point Kinsey-like scale(73). A lower score indicates a more heterosexual orientation.

The Gender Dysphoria Questionnaire for Adolescents and Adults (GIDYQ-AA) is an instrument consisting of 27 questions capturing a range of subjective (13), social (9), somatic (3) and sociolegal (2) indicators of gender identity / gender dysphoria. In study IV we included two of the questions reflecting subjective indications on gender identity / dysphoria as a very brief screening for these issues.

1.7 ADOLESCENCE

Adolescence is a period of biological, cognitive, psychological, sexual and social development. The Oxford English dictionary describes it as the time “between childhood and manhood (14-25 years old) or womanhood (12-21)”. **Adolescence** comes from Latin, *adolescere*, meaning 'to grow up' (74). Its range of duration varies according to different sources and medical, scientific and psychological opinions, but it is usually associated with the teenage years. The end of adolescence and the beginning of adulthood also varies by country and by function. For example, there can be different ages at which an individual is considered (chronologically and legally) mature enough for driving a vehicle, having legal sexual relations, serving in the armed forces or on a jury, purchasing and drinking alcohol, voting, entering into contracts, marriage and finishing certain levels of education. Furthermore, between the ages of 10 and 25, the brain undergoes changes that have important implications for behavior.

In studying adolescent development(75), adolescence can be defined biologically, as the physical transition marked by the onset of puberty and the termination of physical growth; cognitively, as changes in the ability to think abstractly and multi-dimensionally; or socially, as a period of preparation for adult roles. Different specialties have different aspects of adolescence in focus; for example, researchers in neuroscience or bio-behavioral health might focus on pubertal changes in brain structure and its effects on cognition or social relations. Sociologists interested in adolescence might focus on the acquisition of social roles (e.g., worker or romantic partner) and how this varies across cultures or social conditions(76). Developmental psychologists might focus on changes in relations with parents and peers as a function of school structure and pubertal status(76). Some scientists have questioned the universality of adolescence as a developmental phase, arguing that traits often considered typical of adolescents are not in fact inherent to the teenage years.

In this thesis, we are recognizing the physical changes in the sex organs as well as acquisition of social roles (romantic partner) and relations with parents and peers and to some degree also role identity. The latter continue to develop later in adolescence and early adulthood, which is why we have decided to include study subjects up to 25 years of age in the adolescence papers.

2 AIM

Long-term outcome after hypospadias surgery is requested, and necessary as a complement to short and intermediate outcome for evaluation of the results of current surgical methods and postoperative care. The overall aim of this thesis was to evaluate the outcome of patients after surgery performed in early childhood for hypospadias, in and after the changes that occur in puberty. Furthermore, the aims were to contribute to a better care for these patients following acquisition of this knowledge.

More specifically, the aims for **study I** was:

- To investigate if the obstructive uroflowmetry-patterns often seen after hypospadias repair with the TIP-procedure normalized in puberty.

For **study II**, which was part of a collaboration with Stockholm in investigating the results of adults with hypospadias, the aims were:

- To increase the knowledge of the psychosocial outcome in adult men born with hypospadias.
- To assess hrQoL in men born with hypospadias.

For **study III**, the aims were:

- To assess the urological and cosmetical results after surgery for *proximal* hypospadias including complication rates.

And for **study IV**, the aims were:

- To evaluate psychosocial outcome, psychosexual development / behavior, sexual function and satisfaction in comparison to a control group of distal hypospadias patients and age-matched controls.
- To compares results with objective findings on penile length, curvature and sensation in patients with proximal hypospadias.

3 PATIENTS AND METHODS

Table 2. Patients and methods for the different studies at a glance.

	Population	Material	Methods
I	40 boys, Md age 15 y (potty-trained at the time of surgery) / 126 patients operated with TIP between 1999-2003	Uroflowmetry and ultrasound to check for PVR. Miskolc nomograms were used, for comparison of uroflows between different ages.	For tests between two groups Fisher's exact test, Mantel-Haenszel Chi-2 test, Chi-square and Mann-Whitney U-test were used. For change within groups the sign test and Wilcoxon signed rank test were used.
II	167 patients, Md age 34 y, /1030 patients born with hypospadias. 169 age-matched controls from Swedish Population Register, Md age 33 y.	Questionnaire study: Psychological General Well-Being (PGWB), Relationship Questionnaire (RQ) and questions about psychosocial situation.	Descriptive statistics in terms of psychosocial situation, PGWB and RQ. Pairwise tests between groups when appropriate. Associations between two continuous variables were analyzed with Spearman's rank correlation coefficient.
III	39 patients, Md age 16.5 y / 69 patients operated for proximal hypospadias between 1996-2005.	Uroflowmetry results. Prepubertal and adolescent uroflowmetry-results were compared using the Miskolc nomograms. Anatomical evaluation as well as patient satisfaction. Chart review for data on reoperations and other medical conditions.	Descriptive study. All p-values are to be considered exploratory rather than confirmatory. For test between two independent groups Fisher's exact test, Mantel-Haenszel Chi ² test and Mann-Whitney U-test were used. Change over time was tested with Wilcoxon's signed-rank test.
IV	33 patients with proximal hypospadias, Md age 17.5 y 31 patients with distal hypospadias, Md age 19.0 y 25 age-matched controls, Md age 18.0 y	Questionnaire study: PGWB, Body Esteem for Adults and Adolescents (BESAA), Penile Perception Scale (PPS) and questions about psychosocial situation, psychosexual development/ sexual behavior and function.	Descriptive statistics for psychosocial situation, and perceived influence of hypospadias on up-bringing. Pairwise tests between two independent groups were conducted as in Study I. Spearman correlation for test of relation between continuous variables.

3.1 STUDY POPULATIONS AND STUDY DESIGNS

Study I

This study is a continuation of two preceding studies on the same cohort of boys. The initial study (77) compared uroflowmetry results 2 and 12 months after hypospadias surgery with the TIP procedure and also evaluated if a poor uroflow corresponded to an anatomical stricture through calibration of the neourethra. The second study presented intermediate uroflowmetry results in the same cohort of patients after Md 7 years (78). The present study investigated the same cohort of patients, in puberty.

Between 1999-2003, 126 boys with hypospadias had primary reconstructive surgery with the TIP procedure at our institution. The technique, which was introduced by Dr. Snodgrass in 1994, had been used at our clinic since 1997 for distal cases and since 2000 for midpenile to penoscrotal cases. Patients that were potty trained and able to participate in uroflowmetry two months after the surgery were included in the first study, and following this uroflowmetry investigations were performed 1 and 7 years after surgery and after onset of puberty. A total of 40 patients were investigated in puberty, 31 had distal hypospadias and 9 more proximal (midpenile to penoscrotal).

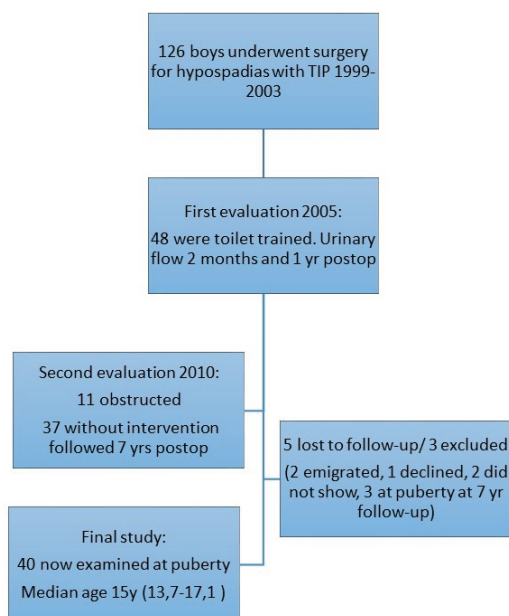


Figure 14. Flow chart of the patient cohort of Study I.

Study II

Study II was performed in collaboration with Stockholm, where former pediatric urologist, Dr. Brodsky had collected a cohort of 571 patients with hypospadias between 1970 and 1984. In addition to this material, patients above 18 years of age at the time of inclusion (2011) receiving the diagnosis of hypospadias in the Stockholm area were added. In Gothenburg, the regional archive (Region Arkivet) has a register of all patients having had surgery between 1966-1994. From this, 78 patients with proximal hypospadias were identified and those currently living in the vicinity of Gothenburg (up to 150 km away, n=48) were contacted and asked to participate in this questionnaire study (and a clinical evaluation, for a subsequent study(39)).

The distribution of phenotypes (which was defined as meatal position preoperatively) was 62.7% (105/167) distal, 24.1% (40/167) mid-penile and 13.3% (22/167) proximal. A drop out analysis showed that the phenotype distribution (among the patients with known phenotype) was comparable to that of the original cohort as well as the age of the patients, which was 34 years of age (19-54 years) and mean follow-up time since surgery was 29 years (6-48 years). Thirteen patients had not had surgery (10 glanular and 3 distal penile).

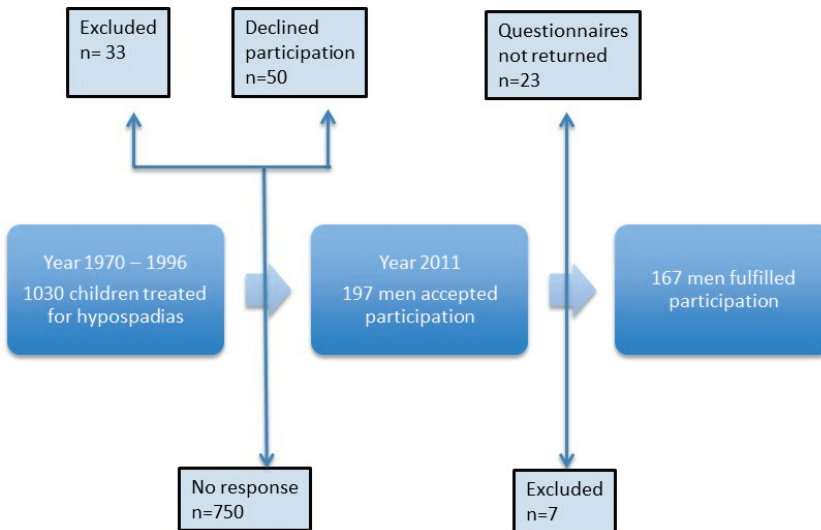


Figure 15. Flow chart of patient cohort for Study II.

For **controls**, men from the Swedish Population Register (SPR) were recruited. Eight age-matched men per patient were contacted (n=1362) with a response rate of 13%. Controls received the same questionnaire as patients minus the hypospadias specific questions. Ninety-one percent of participating controls completed the questionnaire. As this was part of a larger study where a clinical visit was included, and few controls recruited from the SPR were interested in this part, controls were also recruited by advertisement at the medical universities of Karolinska Institute and Sahlgrenska Academy (n=38). The control group had a mean age of 33 years (19-48years).

Study III and IV

Patients: surgical records identified all patients having had primary surgery for penoscrotal to perineal hypospadias, defined intraoperatively as meatal position after degloving considering the division of the spongiosa, between 1996-2005 (n=69). Exclusion criteria were inability to communicate in Swedish language and age <14 years at the time of the study (until the end of 2016), since results after puberty were our main interest.

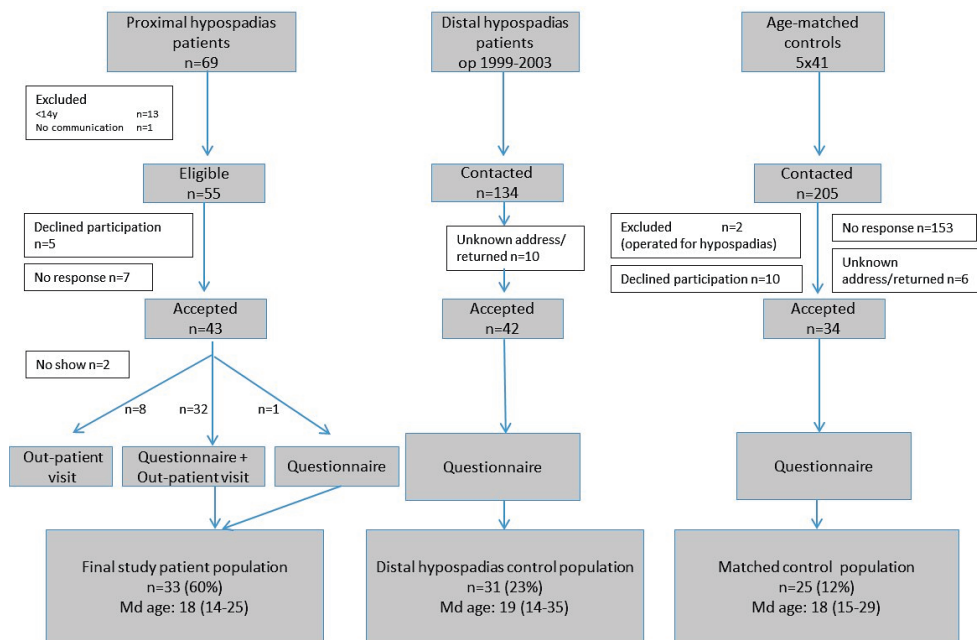


Figure 16. Flow chart for study (III and IV) of participants from identification to study population.

39/55 eligible patients were evaluated resulting in a participation rate for study III of 71%. Median age was 16.5 years (14.0-25.0 years). The study design for study III included a clinical visit with genital examination and questions on satisfaction with penile perception, uroflowmetry and post void residual controls as well as chart reviews.

Thirty-three of fifty-five eligible patients (60%) represent the patient cohort of study IV who answered a questionnaire with the aims of evaluating the psychosocial results, psychosexual development / sexual behavior and sexual function and satisfaction in adolescence after hypospadias repair for proximal hypospadias. Median age in this group was 17.5 years (14.0-25.3).

In study IV, 134 **patients operated for distal hypospadias** with the TIP procedure during 1999-2003 were asked to answer the same questionnaire, 42 accepted and 31 (23%) completed the questionnaire. Five age-matched **controls** from the population register of western Sweden (Västfolket) per participating patient were also asked to answer the questionnaire minus the hypospadias specific questions, 34 accepted and 25 completed the questionnaire.

3.2 METHODS

In **study I**, patients came for a clinical evaluation performed according to a protocol (Clinical Report Form, CRF, Appendix A). The clinical examination evaluated penile length measured slightly stretched from the pubic bone to the tip of the glans, testicular size with an orchidometer and penile curvature in the intervals of 0-10°, 10-30°, 30-60° and 60-90°. Questions regarding voiding function/dysfunction as well as questions on sexual function (erection, ejaculation, intercourse) were asked. Patients also had a uroflowmetry investigation including ultrasound to check for pathological PVR. One to two voidings were recorded, and evaluation was performed on the one with highest maximum flow rate (Qmax). Qmax, voided volume and curve shapes were noted (curve shapes when voided volumes exceeded 50% of bladder capacity). PVR was directly imaged with ultrasound. Abnormal PVR was defined as greater than 20 ml or >15% of bladder capacity according to the International Children's Continence Society(79).

Bladder capacity (BC) is expected to increase continuously with age according to the formula $BC = 30 \text{ ml} + (\text{age} \times 30 \text{ ml})$. A child's penis does not grow in the same continuous manner, but a marked difference is expected in puberty, therefore the radius of the urethra is similarly not expected to increase continuously. Since flow is dependent on the volume and radius of an outlet ($Q = V\pi r^2$), we would expect a higher Qmax due to increased voided volume (and bladder capacity) as the child grows, but this would not necessarily mean that the potentially obstructed urethra improved. Comparison was therefore made according to nomograms where Qmax is related to voided volume and age giving a result in percentile. We defined the uroflow as normal if \geq the 25th percentile and obstructed if \leq the 5th percentile. There are different nomograms available. We chose the Miskolc nomograms(80), in favor of the Toguri nomograms(81) since the latter requires information on body surface while Miskolc nomograms also subgroup according to three age-spans (3-7 years or a body area of $<0.92\text{m}^2$, 8-13 years or a body area $0.92\text{-}1.42\text{m}^2$ and >13 years or a body area of $>1.42\text{m}^2$).

Patient charts were studied regarding surgeries and complications. The number of patients having required interventions due to obstruction of the neourethra was recorded and their uroflowmetry results before and after intervention as well as at puberty were compared. Numbers of fistulas were

also recorded as well as number of patients with Lichen Sclerosus (LS), which is also a known risk factor for strictures of the urethra.

Questionnaires are a method of collecting information in a standardized manner from a large sample of individuals. There are several aspects on this method that deserve some attention. First, before even talking about the construction of the questionnaire, other aspects influence the way it is answered. Circumstances around administration, in what premises, morning or evening, subject being hungry or not, in conjunction to a medical visit or not, if it is performed as an interview face-to face, over telephone, with paper and pen or electronically. When performing a study, an effort of making all these circumstances as similar as possible for all subjects should be made. Second, as part of the construction of the questionnaire, aspects like how the questions are asked, how they are understood etc. are very important. In the development of an instrument a validation process ensures not only that the questions are understood as intended and the instrument measures what it was designed to measure (content validity), that groups expected to have different outcome actually show different outcomes on the test (known-groups validation), but also that the questionnaire is expected to give the same result under similar circumstances (test-retest reliability) and that variables are defined and values on scales defined to enable correct calculations and interpretations (construct validity)(82).

The questionnaires used in study II and IV consisted of validated instruments in combination with questions constructed by our research group. The answers to the latter must be interpreted carefully since they did not go through the meticulous validation process, but they may nevertheless provide interesting information and represent a base for further research.

Study II focuses on the psychosocial results in adults after hypospadias surgery in childhood. It is part of a larger study where urological and cosmetic outcome as well as sexual function and fertility, and psychiatric outcome was assessed. Questions included the areas of family situation, education, occupation, spare-time activities and country of birth. Childhood experiences of bullying and negative influences of hypospadias on relationships, family, friends, partners as well as spare-time activities were also inquired. Occupation was defined according to the Swedish Statistical Database and a study by Frisé et al(68) as “male-dominant” if <25% females and “extremely male-dominant” if <11% females in the profession. Health related QoL was measured using the PGWB and the ability to attach to other people was assessed by the Relationship Questionnaire (RQ).

Study III

The clinical evaluation was performed according to a protocol (CRF for proximal hypospadias, Appendix B) where voiding function was inquired, genitalia evaluated and uroflowmetry including ultrasound for PVR was performed by a urotherapist. Patient satisfaction was evaluated using the PPS/PPPS. HOSE was used to objectify surgical results. A chart review revealed information on gestational week and birth weight, results of genetic analyses, other diagnoses or malformations, surgeries and prepubertal uroflowmetry results.

The severity of hypospadias was defined as meatal position considering point of division of spongiosa intraoperatively. Penile length and curvature was assessed as in study I. Glanular sensation was measured with a cotton swab comparing to the inside of the thigh. “Much more” or “more” was considered normal, “less” or “much less” was considered impaired. Puberty was defined by Tanner stage(83) according to testicular size and hair distribution.

Uroflowmetry results were evaluated in the same manner as in study I. In adolescence a $Q_{max} \leq 10$ ml/s was considered impaired. For comparison of uroflowmetry results to prepubertal results collected from charts the Miskolc nomograms were used.

Study IV used a questionnaire again. The one used for adults in study II was modified in collaboration with a psychologist to suit adolescents. The number of items was reduced from 234 to 108. Health related QoL was evaluated using the PGWB, body esteem using the BESAA, where the subscales for appearance and attribution, but not for weight were used, and penile perception using the PPS/PPPS. Sexual orientation was expressed using a Kinsey like scale and two questions from the GIDYQ-AA were included regarding gender identity/dysphoria. For sexual (dys-)function and psychosexual development, the questions included in the questionnaire were influenced by the DISF-SR, but the whole DISF-SR was not used. In addition, other questions designed by our research group regarding psychosocial factors, psychosexual development/sexual behavior and sexual function were included (Appendix C, translated into English by author).

3.3 STATISTICS

Statistics are used in order to interpret collected data and can be descriptive or analytic (inferential). Most studies start with a descriptive part (e.g. demographics) and continue with the analytic part. Analytic (or inferential) statistics try to make conclusions from observations by calculating the probability of rejecting the null hypothesis (the p-value), odds ratios, hazard ratios etc. All these calculated condensed data assist in reaching a conclusion.

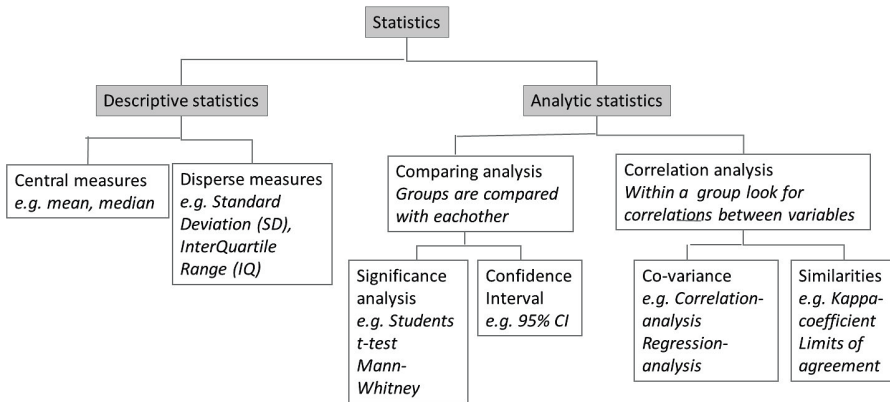
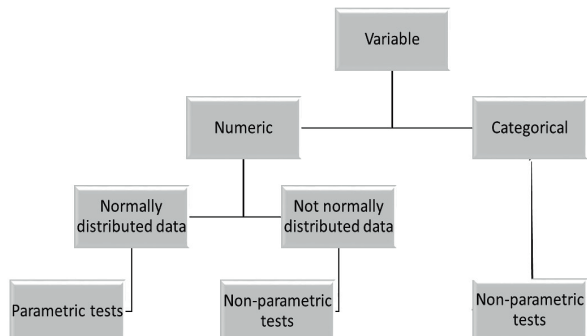


Figure 17. Overview of definition in statistics.

There are an immense number of different statistical methods available, and the decision of which one to use depends on the character of the data the research question to answer.

Data are essentially classified as numeric (quantitative) or categorical (qualitative). Numeric data can be continuous, like temperature or discrete numeric, like number of children. Categorical data can be ordinal (a natural order within, like grades in school; A-F) or nominal (no order). Different statistical tests are suitable for different types of data.

Figure 18. Types of data suitable for different types of statistical tests (simplified).



Parametric tests make assumptions that the sample of data analyzed is distributed in a certain way, where non-parametric tests (or rank methods) make no assumption of the distribution of the sample of data. Examples of parametric tests are Student’s t-test and the paired t-test, and examples of tests used for non-parametric data are Wilcoxon signed rank test and Mann-Whitney test.

The p-value represents the probability that the difference detected is due to chance rather than due to the circumstances presented. The significance level is generally set to a p-value of 0.05, i.e. in 5% of cases the described difference will not be due to the presented hypothesis, but other factors (chance).

A study can be experimental or observational. Experimental studies are often clinical trials, comparing the effect of different treatments or drugs.

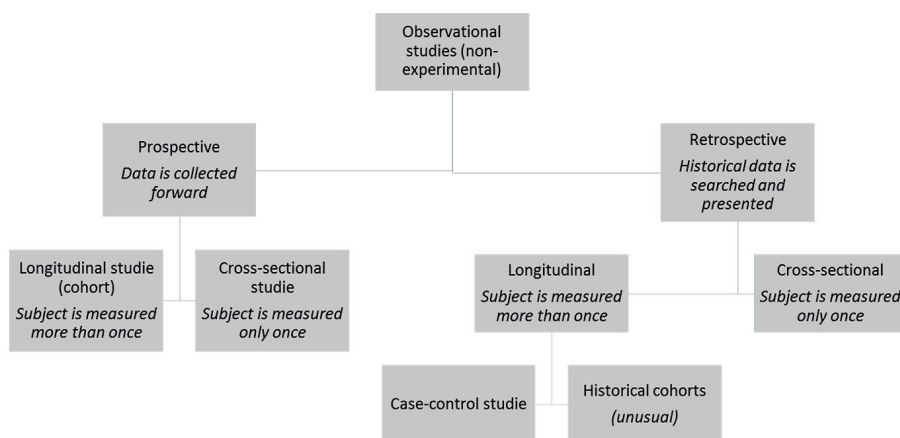


Figure 19. Overview of different types of observational studies.

In this thesis, studies are observational, categorical variables are described by numbers and percentages, and continuous variables by median and range. For pair-wise tests between groups Fisher’s exact test was used for dichotomous variables, the chi-square test for non-ordered categorical variables and Mann-Whitney U-test for continuous variables. All tests were two-tailed and conducted at the 0.05 significance level.

Internal reliability of questionnaires in study IV was evaluated by estimating Cronbach’s α .

In study III, the study was of descriptive nature and statistical testing is hence to be regarded as exploratory rather than confirmatory.

3.4 ETHICAL CONSIDERATIONS

When conducting research, the **Declaration of Helsinki (DoH)** is considered the cornerstone document on human research ethics. It is not legally binding, but constitutes a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA)(84). The fundamental principle is respect for the individual, their right to self-determination and the right to make informed decisions regarding participation in research, both initially and during the course of the research. The investigator's duty is solely to the patient or volunteer, and while there is always a need for research, the subject's welfare must always take precedence over the interests of science and society, and ethical considerations must always take precedence over laws and regulations.

For all the studies included in this thesis, approval has been given from the Ethical Committees of Gothenburg or Stockholm, to ensure these principles were followed.

4 RESULTS

This thesis investigates results after hypospadias surgery in childhood from different angles. Here follows a synopsis of all four studies.

4.1 URINARY FUNCTION

Uroflowmetry

At the time of study I, early postoperative uroflows after the TIP procedure were often described as obstructive although no evidence of strictures were present (33, 85). The long-term results of the TIP procedure after puberty were not well described. Study I showed that the uroflow pattern normalized in the majority of cases. At puberty 95% of patients had normal uroflows, compared to 37.5% one year after surgery and 40% seven years after surgery.

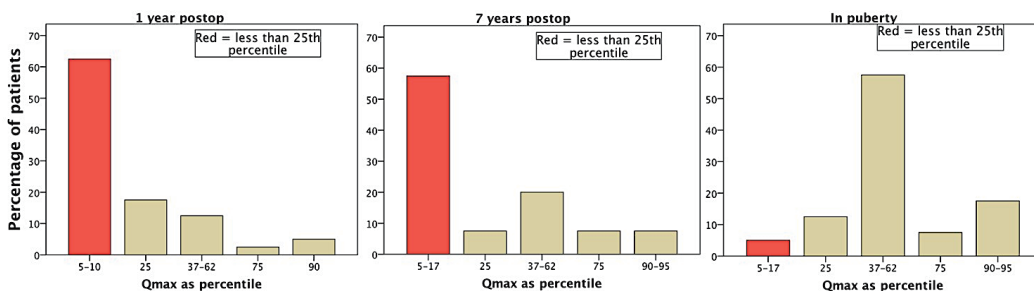


Figure 20. Proportion of normal uroflow findings of patients operated with TIP for distal to midpenile hypospadias (25th percentile and above) at different points of follow-up. Red bars represent flows <25th percentile.

One year after surgery 56% (23/40) had a uroflow considered obstructive ($\leq 5^{\text{th}}$ percentile), 7 years after surgery 40% (16/40) did, whereas at puberty that number was 5% (2/40).

Among patients with *proximal* hypospadias in study III, 85% (33/39) had an obstructive uroflow ($\leq 5^{\text{th}}$ percentile) prepubertally and 19% (7/36) still had an obstructive uroflow in adolescence (TIP, Onlay and Duckett).

Nine patients in study I had required intervention due to obstruction found at calibration. The improvement in urinary flow was seen when analyzing subgroups of distal and more proximal hypospadias, as well as in the group with no intervention and the group having had intervention (dilatation or meatotomy) during childhood.

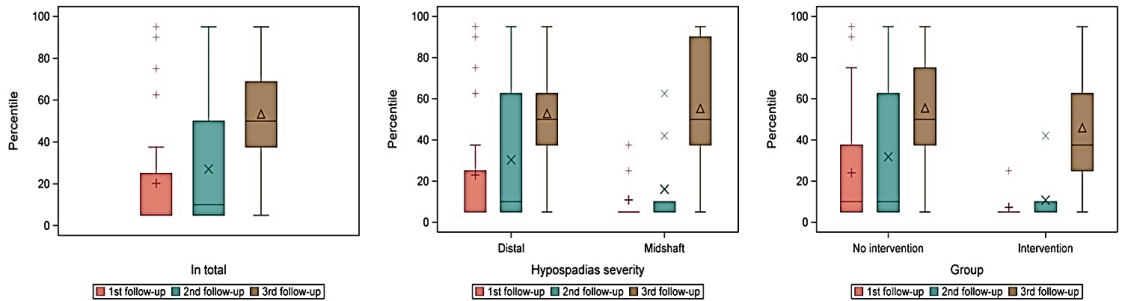


Figure 21. Box plot of uroflometry results according to phenotype and treatment. All improvements were significant from 1 year postoperatively to puberty (distal $p < 0.0001$, more proximal $p = 0.008$, no intervention $p < 0.0001$, intervention $p = 0.0078$)

The urinary flow of the patients that underwent meatotomy due to obstruction at calibration did not improve markedly until puberty, indicating that the changes in puberty, and not the meatotomy per se was the reason for the main improvement.

Symptoms of obstruction / Lower Urinary Tract Symptoms (LUTS)

Of the nine boys requiring intervention due to obstruction found at calibration, eight presented with abnormal urinary stream, and one with recurrent UTIs (urinary tract infections).

Generally, there were few symptoms of obstruction. In study III, five patients had $Q_{max} \leq 10$ ml/s which should awake some symptoms. When comparing the symptoms they described to the group of patients with $Q_{max} > 10$ ml/s no difference was found, and likewise when comparing symptoms in the group of patients with uroflows $\leq 5^{\text{th}}$ percentile with $> 5^{\text{th}}$ percentile, indicating that asking for symptoms alone may not be sufficient if looking for obstruction in this group of patients.

4.2 PENILE CURVATURE

Patients with *distal and midpenile* hypospadias were evaluated without penile curvature in 86% (31/36) and 14% (5/36) had a glanular tilt. Of the 33 that could describe degree of curvature during erection, 9% (3/33) described a slight downward curvature.

Among patients with *proximal* hypospadias, 72% were assessed without penile curvature at follow-up. A curvature was more commonly seen after the TIP procedure for proximal hypospadias (7/14) than after Onlay or Duckett, $p=0.076$ and 0.0062 respectively, but patients having had the TIP procedure had not had a primary decurvature procedure as often as the other groups and curvature was primarily seen in patients operated with TIP without circumcision. Dissatisfaction with penile axis was more common in patients with a penile curvature at follow-up.

4.3 COMPLICATIONS

Among *distal to midpenile* hypospadias operated with the TIP method, 9/40 patients had intervention of their neourethra due to obstruction found at calibrations. In addition, there were 3 circumcisions due to phimosis caused by lichen sclerosus. There were 12.5% (5/40) meatotomies, 5% (2/40) urethrocutaneous fistulas and 10% (4/40) preputial fistulas. Repeat preputioplasties were performed in 4 patients and minor skin correction in one. In all, 65% of patients (26/40) did not require any redo surgery.

Among *proximal* hypospadias patients, 49% had no complications requiring reoperations. The TIP procedure gave rise to significantly fewer re-operations than the Duckett procedure, $p=0.0062$. Thirty-five percent (7/20) of the patients requiring re-operations were re-operated within 3 years after primary surgery, but 30% (6/20) of patients requiring re-operations had surgery done more than 10 years after the primary urethroplasty. Fifteen percent (5/39) had meatotomies and 10% (4/39) had surgery due to urethrocutaneous fistulas. Other reasons for re-do surgery were minor and major skin corrections, internal urethrotomy, perineostoma or re-do urethroplasty. Twenty-six percent (10/39) of patients required more than one re-operation.

4.4 COSMESIS / PENILE PERCEPTION / BODY ESTEEM

Cosmetic outcome was evaluated using HOSE. In study I, information regarding HOSE was available in 33 boys with *distal to midpenile* hypospadias, with a median of 15p (12-16), where 85% (28/33) had a score ≥ 14 p, which is considered an acceptable outcome. For *proximal* hypospadias, HOSE was median 14p (11-16) with 45% (17/38) ≥ 14 p. When evaluating the first item on HOSE, position and shape of the meatus, the majority of patients with proximal hypospadias had a proximal glanular position of the meatus, yet no one reported dissatisfaction with meatal shape or position.

Table 3. The position of the meatus in patients with proximal hypospadias and the satisfaction of their meatal shape and position. No one was dissatisfied with meatal position or shape, regardless if it was distal glanular or not.

		PPS meatus		Total
		Satisfied	Very satisfied	
HOSE meatal position	Coronal	3	1	4
	Proximal glanular	16	5	21
	Distal glanular	2	1	3
Total		21	7	28

Penile length was measured in study I and III. For *distal* hypospadias, median penile length was 11.5 cm (8.0-15.0) and for *proximal* 8.7 cm (4.0-11.0). Dissatisfaction with penile length was not associated to measured penile length in proximal hypospadias, $p=0.74$.

We found no significant difference in satisfaction with penile appearance according to PPS between groups in study IV. Looking at the graph, it is however apparent that only patients with hypospadias scored lower than 6 points.

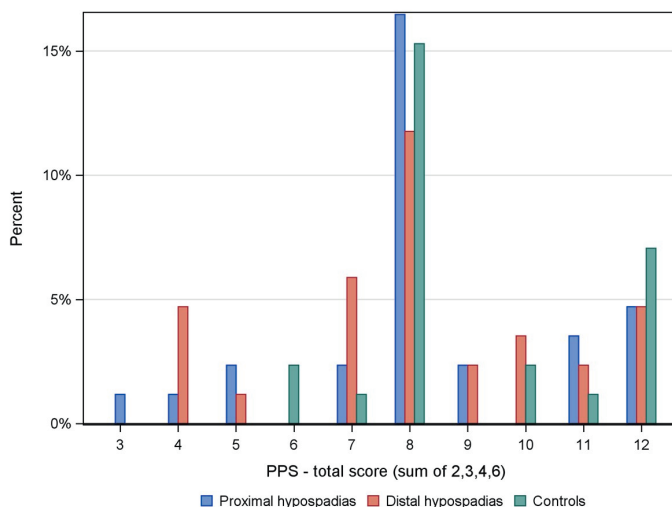


Figure 22. Penile Perception Score (PPS). No controls had <6p. 82% of patients with proximal hypospadias, 68% of patients with distal and 88% of controls scored ≥8p, which seems to be a cut-off.

A higher PPS-score was not associated to have started having sex in any group (p=0.84 for proximal, p=0.30 for distal and p= 0.055 for controls).

Body esteem was evaluated in study IV, where neither distal nor proximal hypospadias showed any difference to controls in the general feelings about one’s appearance (appearance) or in the evaluation attributed to others about one’s appearance (attribution). For adolescents as a total, those with higher scores on views about what other people think about their own looks (attribution) were more likely to have started having sex, p=0.030. This correlation could not be shown in the subgroups of distal and proximal hypospadias. Adolescents scoring low on BESAA for appearance or for attribution also scored low on PPS and on satisfaction with penile length and vice versa.

	Spearman correlation CoefficientsProb[r] under H0: Rho=0 Number of observations	
	Satisfaction on penile length	PPS total score
BESAA appearance	0.48	0.41
	<0.0001	<0.0001
	84	84
BESAA attribution	0.25	0.24
	0.024	0.030
	81	81

Table 4. Spearman correlation between BESAA and satisfaction with penile length as well as PPSscore.

4.5 SEXUAL FUNCTION

Of *distal* hypospadias patients in study I, 98% (39/40) reported erections, 73% (29/40) had ejaculated and 18% (7/40) had had intercourse. In study IV, we found a difference between proximal and distal hypospadias patients in the reported ability to achieve an erection where more *proximal* hypospadias patients answered “sometimes” and “don’t know”, $p=0.032$. More proximal hypospadias patients also reported no ejaculations during orgasm or uncertainty compared to distal hypospadias patients, $p=0.0089$. Proximal hypospadias patients were also more often uncertain of the importance of glanular sensation for pleasure during petting / sex compared to both distal hypospadias patients and controls. No difference was found in the perceived glanular sensation, in the satisfaction with glanular sensation, the ability to have orgasm during petting/fondling or in the occurrence of pain during sex.

4.6 PSYCHOSEXUAL DEVELOPMENT / BEHAVIOR AND GENDER IDENTITY / DYSPHORIA

No differences were found between patients with distal hypospadias, proximal hypospadias and controls regarding sexual interest, time per day spent thinking about sex, number of times being sexually aroused last month, frequency of masturbation, proportion having had sex, age at sexual debut, frequency of intercourse, satisfaction with sexual experiences or ability to enjoy sex. However, 38% (10/26) of patients with proximal hypospadias were uncertain if they were interested in physical contact with a partner, defined as hugging, kissing, French kissing, making out, having sex, compared to 7% (2/31) of patients with distal hypospadias and 17% (4/24) of controls, $p=0.0054$ proximal vs. distal, n.s. vs. controls.

No difference was found in proportion of homo/bi/heterosexual thoughts or behavior between groups.

No difference in core gender identity or gender dysphoria was found between groups.

4.7 PSYCHOSOCIAL OUTCOME / HRQOL

Psychosocial factors and childhood experiences

Both adolescents and adults with both distal and proximal hypospadias had a comparable social situation to controls concerning family constitution and present education and/or working situation. Adolescents with *proximal* hypospadias had more often received specialized tutoring in school (36%) compared to adolescents with distal hypospadias (10%), but not compared to controls (12%), $p=0.024$ and $p=0.068$ respectively. No difference in educational level reached so far in adolescents was found. Among adults, more controls had a university degree than hypospadias patients, $p=0.004$. When analyzing educational level by phenotype, no significant difference was found. A total of 50% of adults with distal hypospadias, and 32% of adults with mid- to proximal hypospadias had a university degree. Adults with hypospadias were more often still living at home with their parents compared to controls, $p=0.001$.

Patients with *proximal* hypospadias more often expressed a request for frequent follow-up, both as adults and adolescents.

Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE)

In adolescents with *proximal* hypospadias, chart review revealed problems in the areas of ESSENCE that had led to consultation or further psychiatric evaluation during childhood in 36% (12/33). The actual number might be even higher since some patients were referred from hospitals in a different region and therefore possibly were treated for their psychiatric problems at a different hospital. Charts were not studied for patients with distal hypospadias or controls but comparing to literature, the number of boys having had symptoms of ESSENCE up until 18 years of age is 13% in Sweden (54).

PGWB

Health related QoL measured by PGWB was comparable between patients and controls, both in the study of adults and the study on adolescents and we found no differences between proximal and distal hypospadias.

Adolescents scored a mean total PGWB of 79.1 (SD 12.4) (proximal), 76.5 (SD 13.1) (distal) and 77.3 (SD 10.4) (controls), whereas adult patients scored 82 (SD 15.3) and adult controls 85.6 (SD 10.8).

Dimenas et al provides information on expected scores for Swedish men, however, there is no reference for teenagers in this study. The average score on PGWB in men 20-30 years old in Sweden is described to be 82 with an accepted range of 78-83 depending on sex and age(86).

5 DISCUSSION

5.1 DISCUSSION ON FINDINGS

There have been two main focuses during the work of this thesis: the long-term outcome after the TIP procedure, and the long-term outcome after surgery for proximal hypospadias. Long-term outcomes are not possible to assess until after puberty. We have awaited puberty and adolescence to be able to assess outcomes of techniques still in use today. In assessing psychosexual development and behavior, we believe doing so during the time these changes occur, minimizes the risk of recall bias.

TIP. The studies in this thesis have shown that *urinary flow* (function) for the absolute majority of patients will improve markedly after puberty, but impaired uroflows are more common for patients with proximal hypospadias. These findings are in line with those of Hueber et al(35), as they found 20% with still obstructive flows (<5th percentile) in patients >13 years of age with penoscrotal hypospadias operated with the TIP procedure, compared to our numbers being 23%. This number is considerably higher than for distal hypospadias where 5% were obstructive at puberty, according to study I. The long-term results regarding urinary flow after the TIP procedure are reassuring warranting continued use of the technique in spite of the obstructive uroflow pattern seen early on after TIP. The reason for this improvement is not investigated, but presumably an increased radius is one factor. This would indicate that the hypoplastic urethral plate grows along with the boy to create a sufficient neourethra in puberty. However, study III also showed an increased risk for recurrent penile *curvature* in proximal hypospadias after the TIP procedure. This could be due to an, in this regard, insufficient growth of the urethral plate. More likely, however, it is a consequence of trying to preserve the foreskin. In these cases a less meticulous dissection is performed, possibly leaving some dysplastic tissues responsible for this recurrence. Furthermore, when preserving the foreskin no plication is performed. Either way, this risk must be taken into consideration so that the TIP method without circumcision, is not chosen if there are any doubts regarding sufficient curvature correction. With the results from this study, it could be true that a preputioplasty is not recommended in long-TIPs because of the increased risk for recurrent penile curvature in adolescence and the increased risk for reoperations.

Proximal hypospadias The satisfactory uroflows found in puberty were notably after a considerable number of re-operations. *Complications*

requiring surgery was common, which is a well-known risk after surgery for proximal hypospadias. Örtqvist et al reported 32% fistulas in proximal hypospadias(39), Aulagne et al reported 41% requiring more than the initial one- or two-stage repair(87), Chertin et al reported 61% complications among proximal hypospadias(88). We found that 52% of patients with proximal hypospadias had required re-operations, more commonly after the Duckett procedure, where 72% had required re-operations. Arguably, patients requiring the Duckett procedure had the worst starting conditions with the most severe hypospadias, which in itself might yield a greater risk for complications. All of the perineal hypospadias were reconstructed with the Duckett procedure and the TIP procedure was only used for patients with penoscrotal hypospadias, however, the Duckett procedure was also used for a few patients with penoscrotal or scrotal hypospadias. Nevertheless, it is true that these groups are not comparable. The take home message is instead that if circumstances require dividing the urethral plate, it is wise to expect and prepare patients and parents that re-operations are likely to be needed. Furthermore, only one third of the patients requiring reoperations had their latest reoperation within 3 years of the primary urethroplasty and one third had their latest reoperation more than 10 years after the primary operation, illustrating the need for follow-up through adolescence.

Table 5. Number of patients with different phenotypes having had different types of reconstruction in study III.

	TIP	Onlay	Duckett	Total
Penoscrotal	14	12	3	29
Scrotal	0	2	2	4
Perineal	0	0	6	6

Penile perception, measured with PPS was not significantly different between patients with proximal hypospadias, distal hypospadias and controls, however patients with proximal hypospadias scored lower when questioned about satisfaction with penile length. Many previous studies have described a decreased satisfaction with cosmetic outcome(46, 47, 50, 88), sometimes defining that the decreased satisfaction is due to dissatisfaction with penile length, which would correspond to our findings. However, patients in study III and IV were otherwise satisfied with penile appearance. It is possible that this reflects a better cosmetic outcome following improved surgical

techniques compared to previous results, which, in that case, is encouraging.

Importantly, boys in this study were equally satisfied with meatal position and shape as controls, even as meatal position was mainly proximal glanular or coronal. Perhaps pediatric urologists in the future should stress too much about glans dehiscence, and possibly, the ruling of if a hypospadias repair is successful does not have to depend on meatal position, as long as it is in the vicinity of the tip. This could also motivate a reevaluation of the ambition to always achieve a distal glanular meatus.

Penile length continues to be a concern for patients with proximal hypospadias and patients with proximal hypospadias do have a shorter penile length(39, 89). We did, however, not find a correlation between penile length and satisfaction with penile length or appearance in patients with proximal hypospadias. This could be a reflection of that most people compare themselves to what they consider normal, not to those less fortunate, but it could also indicate that other psychological aspects, such as self-esteem, acceptance and coping play an important role. However, not many patients claimed they had had or would have wanted psychological support. Perhaps the affirmation and support needed is even easier to embrace in this age when coming from the surgeon.

Regarding curvature, no difference was found between patients with proximal hypospadias in adolescence having had and not having had a primary decurvature procedure. There are at least two possible explanations for this. Either, all patients were corrected so that there was no persistent penile curvature in any of the cases after the primary operation, and all patients, whether having had an additional decurvature procedure or not, risk a recurrence of penile curvature with the growth in puberty. Alternatively, the surgeon was influenced by the parents' desire to preserve the foreskin, which could affect subjective assessment of sufficient correction of the initial curvature. Likewise, in Onlay the surgeon could have been affected to accept some persistent curvature in order to salvage the urethral plate, especially since at the time, there were many reports of risking loss of glanular erection when transecting the plate. Speaking in favor of this interpretation is that all patients after the Duckett procedure were without penile curvature at follow-up. Implementing a more proactive approach regarding penile curvature, with this knowledge in mind, would mean to more often perform a circumcision and plication if TIP is considered for a proximal hypospadias, and to consider transecting the urethral plate when that is not sufficient, which increases the chance of providing a straight penis in adolescence and possibly also to gain some penile length.

Psychosexual development / sexual behavior was found to be comparable in most parts between patients with proximal and distal hypospadias and controls in study IV. Previous evaluations of these aspects have come to different conclusions, but several have described an increased inhibition in seeking sexual contact, especially among proximal hypospadias (37, 65, 89, 90). In our study, one third did not know if, or were not, interested in physical contact with others, defined as kissing, hugging, making out, having sex. We also found an increased number of patients with neuropsychiatric problems, as also described by Butwicka et al(52). These findings could be interrelated, but need to be further studied. In our study, 12/14 with neuropsychiatric problems answered the questionnaire and two of them affirmed interest in physical contact, the rest did not respond, were uncertain or negative. Other aspects of sexual behavior such as choice of sexual partner were no different than controls. In accordance with previously described problems more common for patients with hypospadias(91), a few of the patients with proximal hypospadias in study IV also described anejaculation and occasional erectile difficulties. Since the patients did not address these problems at the clinical visit, and uroflow results were good, no further investigation has been performed.

In summary, follow-up after hypospadias surgery has historically in many cases consisted of only early post-operative visits. Traditional thinking has been that any significant complications will have presented within the first years after surgery and therefore further follow-up is not cost-effective or necessary. It was also presumed that patients would seek consultation for the few problems that may arise later. A concern has also been that repeatedly bringing the genital anomaly to the patient's attention could instead cause psychological concerns (17). However, our studies show that this assumption may need to be reevaluated. Patients with urinary obstruction don't reflect upon it being abnormal, especially if flows have always been low as often after hypospadias surgery, and therefore they won't seek consultation for it. Surgery for complications after proximal hypospadias reconstruction was done in 65% of the cases after more than 3 years postoperatively. Especially patients with proximal hypospadias welcome more medical follow-ups and have perceived the follow-up visits as positive. In combination with the finding of proximal hypospadias having had more specialized tutoring in school and more neuropsychiatric symptoms we find it important to offer consultations during adolescence. For these appointments the anticipation must be that extra time might be required for supporting, explaining and confirming the ability and probability of having a normal and satisfactory love life.

5.2 METHODOLOGICAL CONSIDERATIONS

Conclusions that are made for a population aren't necessarily true on an individual basis. But also on a group level, factors can influence if the conclusions drawn are valid. *Internal validity* is the extent to which a causal conclusion based on a study is warranted, and for that a study must minimize systematic error (or 'bias'). Random errors, instead, arise due to random variability of data. *External Validity* describes the extent to which the results of a study can be generalized to other populations.

Internal validity

Examples of systematic errors are: selection bias, drop-out, history of other events, reliability of measures and procedures, low power, order effect, multiple tests of significance and confounders. These will be discussed as they relate to our studies in the following section.

Selection bias

Those selected for analysis may differ from those eligible regarding the association between exposure and outcome. Patients choosing to participate might be particularly dissatisfied, wanting to express their discontent or taking the opportunity to finally have a consultation for their problems. On the other hand, the opposite could be true, if very satisfied, not ashamed you might be more likely to participate. The best way to handle selection bias is to perform a randomized controlled trial (RCT), however, this is not always an option. The participation rate in study I and III were high, so selection bias was not considered a great risk here.

In case-control studies, selection bias might become more pronounced since the response rate to different types of investigations have declined during the last decades, and not uniformly so over all groups of the population. Factors that favor participation are if the study investigates an issue particularly salient to the participants' lives. Participation rates among cases, in case-control studies, are hence consistently higher than among controls(92), as also found in study IV. Furthermore, individuals with a higher socioeconomic status, a higher education, and a current employment are more likely to respond to research inquiries(92). This could partly explain the finding of a higher educational level in study II. The participation rate, especially for controls, in study II and IV were low, and selection bias is an obvious risk. The rate is however in line with the majority of other studies in the field of

long-term follow-up. According to the selection bias patterns previously described, the controls would be expected to have higher educational levels, perform better in school and have a higher socioeconomic status. This could partially explain the finding that patients with proximal hypospadias had more specialized tutoring in school. That finding is however in line with a higher prevalence of neuropsychiatric symptoms, which was found in comparison with the normal population.

Confounders. The distinction between “confounding” and “selection bias” is sometimes blurred in the term “selection confounding.” Hernán et al defined “confounding” as referring to the presence of common causes and “selection bias” as referring to conditioning on common effects (93). Possible confounders in our studies are e.g. lichen sclerosus for obstructive uroflow or neurogenic bladder dysfunction for LUTS. For affected psychosocial and sexual outcome possible confounders are having had genital surgery or different degrees of hypospadias. We have tried to control for confounders in our studies, in analyzing different phenotypes of hypospadias separately and describing the frequency of patients with LS. It would have been interesting to have compared psychosexual results to a group of patients having had circumcision for phimosis alone, which was attempted in study II, however, the phimosis group was younger than the patient group, making comparisons difficult in this regard. Hypospadias phenotype is a difficult confounder to consider, because even different degrees of proximal hypospadias behave differently, which e.g. gives the premise of what surgical technique to use. In study III we therefore state clearly that statistics are descriptive and all statistical testing should be regarded as exploratory, not confirmatory.

Reliability of measures and procedures. One problem with hypospadias research in general is different classifications of phenotypes. We have described the phenotypes according to meatal positioning during surgery after degloving in study I, III and IV. In study II, only preoperative meatal position was available, which is a more uncertain definition. A written CRF with instructions were used to minimize differences in measurements between assessors. Questionnaires represent a type of qualitative research and present different risks of biases. There is inter-rater reliability if an assessor is performing the evaluation. There is the test-retest reliability to verify that the same answer will be given under the same circumstances at a different point of time. If different parts of a questionnaire addresses the same area of interest, the internal consistency reliability can be assessed with Chronbach's α , which measure if there is consensus between the outcomes in these areas. We performed Chronbach's α – tests in study IV. In our study, ”self control” did not reach what is considered acceptable internal consistency reliability

(>0.7). All participants were given the same instructions on how to answer the questionnaires, however, a few answered a written version instead of the web-based questionnaire, possibly influencing results (participants becoming more bored, tired, disinterested, fatigued). Electronic programs have been documented in individual experiments and in reviews to have more complete item response rates than the various paper and pencil methods(94). Other advantages have been described as a high potential for willingness to disclose sensitive information, a low potential for social desirability bias (the responders wanting to present themselves in the best possible light) compared to face-to-face interviews, a low potential for yes-saying bias and low potential for question order effects. A disadvantage is a low potential for item response/completion of questionnaire and a low potential for a more complete population(95).

The majority answered the questionnaire in connection to the clinical examination, which could also influence the answers (being made aware of certain issues).

Low power. Small sample sizes may have insufficient power to detect a difference, even if it is there. This is a problem in many studies in the field of pediatric urology and surgery. In our studies, when analyzing subgroups, the sample sizes were particularly small; hence there could actually be a difference even if we couldn't detect one.

Multiple tests of significance. The more significance tests you conduct on one set of data, the more likely you are to claim that you made a significant finding when you instead capitalize on chance fluctuations. In study IV, we used the Eklund-Seeger formula(96) to estimate upper limit of expected number of false significances for tests performed in the groups 'psychosocial outcome', 'psychosexual development' and 'sexual function and satisfaction' respectively. The results suggest that in the 'sexual function and satisfaction'-group, 3/13 significant findings might be due to chance. Furthermore, the finding that patients with proximal hypospadias more often had wanted psychological support might be due to chance as well as the uncertainty of desire for physical contact found in patients with proximal hypospadias.

External validity

To determine whether the conclusions drawn from the results of this study population are also valid for other populations one needs to consider which of

the results are applicable, for whom and under what circumstances can these results apply to others? The surgical methods used in study I, III and IV are to a large extent used even today around the world. In our clinical praxis, we have switched from the Duckett procedure to a 2-stage procedure when the urethral plate is insufficient for reconstruction, with the hopes of decreasing complication rates. In study III and IV, we decided to include all proximal hypospadias patients, including those with a known genetic cause and those initially investigated due to unknown sex. It is possible that patients with a measurable abnormality in androgen function have a different impact throughout life of their hypospadias. However, we wanted to describe the group of proximal hypospadias as an entity and have also described the results of this group separately. In the questionnaire parts (study II and IV) the participation rate was low, which affects the generalizability. A dropout analysis performed of the study group in study II, III and IV showed that main characteristics were not significantly different from those of the initial population.

Cultural influence may also have an impact on external validity. In Sweden, the tradition is to preserve the foreskin and being circumcised meant being abnormal during these boys' childhood. With an increasing proportion of immigrants and people with other cultures now living in Sweden, being circumcised today is not as different as it was for the patients in this thesis. In other countries being circumcised is the norm so some of the issues our study population faced are not valid in other countries.

6 CONCLUSIONS

Study I

The obstructive urinary flow after TIP repair for hypospadias can normalize with time and penile growth. Unless symptoms occur, a conservative approach seems preferable.

Study II

Patients treated for hypospadias have a good HRQoL, can be expected to have a normal psychosocial life, marry and have children to the same extent as controls. Patients with proximal hypospadias needed or had been in need of more psychological /sexological support.

Study III

Patients operated for proximal hypospadias have a good urological outcome, although reoperations are common and many are performed late, emphasizing the need for follow-up through adolescence. Penile length and penile curvature (when present) is of concern for patients with proximal hypospadias. The TIP procedure more often resulted in a recurrent penile curvature after puberty, possibly due to the fact that a plication was not performed as often, a preputioplasty was performed in half of the cases, or insufficient growth of the hypoplastic urethral plate.

Study IV

Results in adolescence regarding psychosexual development and sexual function were overall encouraging for patients with proximal hypospadias, however one third expressed uncertainty regarding desire for physical contact. Specialized tutoring in school was also more frequent. Together this advocates for continuous follow-up through upbringing allowing extra time for age-appropriate information and support for patients with proximal hypospadias.

7 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Clinical implications

Throughout the work with the patients that constitutes the basis for this thesis, it has become evident that the adolescent clinical visits have been very appreciated by the patients. Often these visits were in the late afternoons or evenings, which was also an advantage for patients, who did not have to miss out on school or explain the reason for that. Many young men were hesitant, but had issues they wanted to discuss. Surgeons not often consider themselves as having the responsibility for psychological support, but in this case, we believe surgeons can make a difference for these patients by providing that. All patients with hypospadias should be offered a clinical follow-up with a hypospadias surgeon at approximately 15 years of age. For patients with proximal hypospadias, follow-up should be offered more frequently in and around puberty with an additional visit after 15 years if the boy has not yet reached maturity to address sexual questions. Knowledge of and having the anticipation, that these patients might need specialized support, just as many of them have needed in school, can make a huge difference. And with that support they can have the same outcome as their peers.

We have changed our surgical method for proximal hypospadias patients where the urethral plate requires transection, from Duckett to a two-stage graft repair, even before the results of Study III. If the complications rate will be lower with this method remains to be seen, however, the fact that the Duckett procedure required many late reoperations strengthens us in the belief that a two-stage repair is preferable.

Future perspectives

The care surrounding patients with hypospadias has changed over the years and is continuously changing. Currently, two subjects are frequently discussed, timing of surgery and refraining from surgery in mild cases. At present, surgery for hypospadias is conducted between 12-18 months of age. Some voices are advocating postponing surgery until the child can give

informed consent. Mureau et al showed a more negative genital appraisal when surgery was performed between 3-6 years of age as compared to between 0-3 years and > 6 years(46) and furthermore, the later the treatment was completed, the later patients began to make their first sexual contacts(47). Schönbacher found that the later corrective surgery was completed, the more likely the patients became insecure with regard to gender-role behavior (median age at final operation 2.92 (0.78–12.29), measured with questions regarding hobbies, sports, games, friends, clothing, identity, and self-attribution of gender characteristics)(64). Although we now can describe the results of surgery performed so far, there is yet no consensus on what age is optimal for hypospadias repair, and possibly, by changing age of reconstruction we affect other psychological mechanisms in processing being born with and treated for a genital malformation. Future research will have to contribute and through comparison hopefully a consensus can be made on best timing. Adult urologists dealing with hypospadias cripples and problematic strictures point out the advantages of not operating mild forms of hypospadias. Very little research is performed on patients with non-corrected hypospadias. Schlomer et al presented data on 52 patients with untreated hypospadias who reported worse outcomes (evaluated using the Sexual Health Inventory for Men and International Prostate Symptom Score, more ventral penile curvature and resulting difficulty with intercourse, worse satisfaction with meatus and penile curvature and more sitting to urinate) compared with non-hypospadiac men. Mild untreated hypospadias had fewer adverse outcomes than severe hypospadias(97). To evaluate if results after surgery for distal hypospadias is superior to results after untreated hypospadias, more studies are warranted. Parents of patients with the mildest form of hypospadias are, in our clinical practice today, informed that a minor difference in appearance will probably not affect their boy at all. A surgical procedure would therefore be purely for cosmetic reasons, which the boy himself could decide if he wants when he is old enough to express himself.

“The poets did well to conjoin music and medicine in Apollo, because the office of medicine is but to tune the curious harp of man's body and reduce it to harmony.”

— **Francis Bacon**

From “The Advancement of Learning” published in 1605.



Drawing by author.

ACKNOWLEDGEMENTS

This project would not have been possible without all the amazing young men, **patients with hypospadias and controls**, who generously contributed with their time and thoughts on past and present experiences. THANK YOU!

Gundela Holmdahl – my main supervisor. I feel privileged to have gotten the opportunity to complete this thesis under your supervision! You are such an inspiration, as a surgeon, as a doctor, as a leader and as a person! I truly admire your brilliance. You are always "spot on", whether questions relate to clinical work, research or everyday life.

Professor **Ulla Sillén**, my co-supervisor, for providing mental support and financial stability.

Sofia Sjöström, for tremendous input and help during study III and IV. Thank you for being like an extra co-supervisor, for being such an inspirational researcher and for all the fine words of encouragement.

Kate Abrahamsson, my chief and professor for supporting me and giving me the opportunity to carry on with this work.

Monika Doroszkiewicz, for your invaluable support as a research assistant and for lifting my spirit when needed.

The other part of our pediatric urology team: **Pia Löfgren** and **Josefin Nordenström**, for the great times working together, past and future. Thank you for supporting me and carrying the greater clinical weight during the finishing of this thesis. IOU.

Sahlgrenska Academy and the **Department of Women's and Children's health**, for giving me the opportunity to become a PhD student.

My co-workers at the **Pediatric Uro-Nephrology Centre (PUNC-K)**. You make working here a joy.

Agneta Nordenskjöld and **Lisa Örtqvist**, my Stockholm colleagues. The collaboration with you has been so fun and easy. Thank you for sharing both knowledge and support.

Lennart Sjöholm, my first mentor, for your careful guidance and tender way towards little patients and young doctors. You are the reason I ended up in pedes in the first place.

My grandmother, **Anny**, who yearned for knowledge and encouraged all the women in her surrounding to get a higher education. I believe I have her to thank for a lot. I wish she could have been here today.

Mom and Dad, for always supporting me and believing in me. Your unconditional love has made all the difference.

My brothers, **Magnus** and **Peter**, for teaching me how to fight ;)

My dearest friend and cousin, **Åsa**, for sharing all those moments.

Jennifer, Tim, Jessie and Niki, for introducing the term "chosen family" to me. You are chosen family! I am so happy to be part of this life journey with you. You inspire me!

Fridolf, Otto and Greta - my children, the greatest joys of my life. Thank you for the gift of being in your presence. You make my life filled with all that, which is *life*, and bring great meaning to it all.

Dan - my husband, thank you for being you: loving, confident, calm, and for your ability to focus on and enjoy the good things in life. Thank you for supporting me through everything, and for being the most amazing father to our children.

This thesis was supported by grants from the Gothenburg Medical Society (Göteborgs Läkaresällskap), Vera and Hans Albrechtsson's foundation, Petter Silfverskiöld's Memorial Fund, Wilhelm & Martina Lundgren's Memorial Fund and governmental grants to the Sahlgrenska University Hospital through the ALF agreement.

APPENDICES

- A. CRF for study I, TIP at 15 years of age
- B. CRF for study III, proximal hypospadias
- C. Questionnaire for study IV (translated to English by author)

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Appendix A.

CRF Postop efter TIP pubertet

Patientnummer:

Datum:

Allmänt: Intro ang.
hypospadi, minnen,
vad undersökningen
består av etc.
För def- se manualen!

Kommentarer (minnen från op,
uppväxt...) _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Totalt antal operationer samt typ inkl sondering i narkos ____

Kommentarer: _____

Mått: (us i liggande, se manualen)

Penis

- längd
- bredd
- omkrets
- kurvering

Mått

- ___ cm
- ___ cm
- ___ cm
- 0-10⁰ 10-30⁰ 30-60⁰
- 60-90⁰ glanstipp

Glans

- längd
- bredd
- omkrets

Mått

- ___ cm
- ___ cm
- ___ cm



Skiss penis sedd från sidan



Skiss penis sedd framifrån

Meatus
Kryssa i platsen för meatus

Utseende u.a atypisk (rita):

Avstånd

corona-meatus: _____ mm
 meatus- penis bas: _____ cm

Läge toppen av glans
 ventralt glandulärt
 koronalt
 distalt penilt
 penilt
 skrotalt

Fistel: ja
 nej

Läge: _____

Preputium

- circumciderad finns
- kluvet
- cirkulärt
- lätt att retrahera
- fimosis
- förhudsfistel

Tecken till BXO
 ja nej
 lokal:

Testiklar

testiklar i skrotum bilat
Läge testikel höger:
 saknas
 subcutant buk
 inguinalt
 scrotalt
volym höger: _____ ml

Läge testikel vänster sida
 saknas
 subcutant buk
 inguinalt
 scrotalt
volym vänster: _____ ml

Scrotum

- symmetrisk, normal
- bifid skrotum

Transposition

- nej
 - mild partiell
 - svår partiell
 - total
- Tecken till varicocele
 ja nej

Pubisbehåring ja nej

rita in på skissen

Ärrighet

- Nej
- Ja (rita på skissen ovan)

Flödeskurva/resurin utfört

Maxflöde: _____ ml/s Flödestid: _____ sek

Miktionsvolym: _____ ml

Flödeskurva (ringa in): klocka, plåtå, fraktionerad

Resurin: _____ ml

Miktionsanamnes

Dagtorr: Ja ålder när? _____ Nej

Nattorr: Ja ålder när? _____ Nej

Beskriv ev dagläckage: _____

Frekvens dagläckage: dagligen varje vecka mer sällan

gleskissare ≤ 3 miktionser /dag frequency ≥ 8 miktionser/dag nocturi

svag stråle lång, hård stråle krystning efterdropp lång miktionser

Urinvägsinfektion som antibiotikabehandlats

Antal utan feber _____ Antal med feber (>38 grader) _____

Kommentar _____

Sexualanamnes

Erektion: Ja Nej Vet ej

Om erektion:

Rak penis vid erektion Ja Nej Vet ej

Penis kurverad nedåt vid erektion Ja Nej Annan kurvering: _____

Utlösning: Ja Nej

Sexdebut: Ja Nej

Kommentar _____

Fria kommentarer:

Undersökning utförd av:

_____ datum _____

MANUAL för us vid prospektiv studie manlig DSD

Definiton av begrepp

Operationstyper:

Uretra: TIP =tubulariserad inciderad platta fritt transplanterat – kommentera vad vask lambå - kommentera om onlay eller tubulariserat graft 2seans

Upprättning: plissering ja/nej/vet ej -kommentera Nesbit eller Baskin inlay ventralt corpora – kommentera vilken graft

Penis undersöks med patienten liggande på britten

Längden mäts mot höger pekfinger med fingerspetsen in dikt an mot symfyfen och i sträckt läge av penis och längden stämmer av mot fingret som jämförs med en linjal liggande på bordet. Mät gärna undersökarens finger innan!

Bredd mäts mitt på skaftet liksom omkrets, mäts med ett snöre och kontrollera måttet mot linjalen.

Kurvering i vila anges höftat i intervallet 0-10, 10-30, 30-60, 60-90 grader. Specialfall tipp av själva glans med rakt penis skaft.

Mått penislängd vid erektion efterfrågas. Mätes om möjligt vid undersökningen.

Mått på glans mäts med snöre och jämförs mot linjalen på bordet.

Bredd mäts på bredaste stället.

Vid 14 år viktigt fråga om glans är hård vid erektion av penis!

”Penis sedd från sidan” resp. ”Penis sedd framifrån” ger utrymme att rita för att förtydliga till exempel kurvering eller ärrighet.

Meatus: Utseende på meatus om ej slitsformig.

Mått corona till meatus närmaste kant, mates med snöre som ovan.

Mått meatus kant och ner till penoscrotalvinkeln, mätes med snöre som ovan.

Läge kryssas i men kan också läggas in i en eventuell skiss.

Ange om det finns en fistel, var den är belägen, enligt listan på meatus läge samt ange eventuellt hur stor mynningen är.

Preputiet: kan vara borttaget, oopererat dvs. kluvet eller ihopsytt med en plastik dvs cirkulärt.

”Tecken till BXO” dvs vitaktig vävnad, här anges om det finns misstänkta områden men vi har inte krav på PAD-verifikation. Ange även var dessa förändringar finns och/ eller markera i skissen.

Testis palperas i liggande, ange storlek med hjälp av orchidometer.

Scrotum undersöks i stående, beskriv om scrotum är “normal” eller bifid. Kommentera om det finns annan patologi.

Graden av **penoscrotal transposition** uppskattas till mild eller svår partiell samt total efter hur mycket av scrotum som är belägen ovanför penisbasen.

Om tydliga **ärr** ses bör de beskrivas och ritas in på skissen och fotografierna bör tas så de syns.

Appendix B.

CRF Postop efter djupa hypospadier, pubertet

Allmänt: Intro ang. hypospadi, minnen, vad undersökningen består av etc.
För def- se manualen!

Kommentarer (minnen från op, uppväxt...) _____

Operationsdatum och vad: _____ Ålder vid op (mån): _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Operationsdatum och vad: _____

Totalt antal operationer samt typ inkl sondering i narkos ____
Kommentarer: _____

Preop testosteron Ja Nej

Prematur, antal v: _____ Födelsevikt: _____ g

Flödesundersökning vid ca 5 åå.

Flödeskurva/resurin

utfört _____

Maxflöde: _____ ml/s

Flödestid: _____ sek

Miktionsvolym: _____ ml

Flödeskurva (ringa in): klocka,
platå, fraktionerad

Resurin: _____ ml

Ålder vid us (mån) _____

Patientkod:

Datum:

Aktuell ålder(ååmm) _____

Mått: (us i liggande, se manualen)

Penis

- längd
- bredd
- omkrets
- kurvering

Mått

- _____ cm
- _____ cm
- _____ cm
- 0-10⁰ 10-30⁰ 30-60⁰
- 60-90⁰ glanstipp

Glans

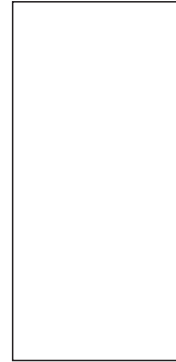
- längd
- bredd

Mått

- _____ cm
- _____ cm



Skiss penis sedd från sidan



Skiss penis sedd framifrån

Meatus

Kryssa i platsen för meatus

Utseende

- u.a
- atypisk (rita):

Avstånd

- corona-meatus: _____ mm
- meatus- penis bas: _____ cm

Läge

- toppen av glans
- ventralt glandulärt
- koronalt
- distalt penilt
- penilt
- skrotalt

U-fistel: ja nej

Läge: _____

Preputium

- circumciderad
- finns
- kluvet
- cirkulärt
- lätt att retrahera
- fimosis
- förhudsfistel

Tecken till BXO
 ja nej
 lokal:

Testiklar

- testiklar i skrotum bilat
- Läge testikel höger:
 - saknas
 - subcutant buk
 - inguinalt
 - scrotalt
- volym höger: _____ ml

- Läge testikel vänster sida
 - saknas
 - subcutant buk
 - inguinalt
 - scrotalt
- volym vänster: _____ ml

Pubisbehåring ja nej

rita in på skissen

Ärrighet

- Nej
- Ja (rita på skissen ovan)

Scrotum

- symmetrisk, normal
- bifid skrotum

Transposition

- nej
- mild partiell
- svår partiell
- total

Tecken till varicocele

- ja nej

Sensibilitet glans

- ++++
- ++
- +(mots lår insida)
- 0

Flödeskurva/resurin utfört

Maxflöde: _____ ml/s Flödestid: _____ sek

Miktionsvolym: _____ ml

Flödeskurva (ringa in): klocka, plåtå, fraktionerad

Resurin: _____ ml

Miktionsanamnes

Dagtorr: Ja ålder när? _____ Nej

Nattorr: Ja ålder när? _____ Nej

Beskriv ev dagläckage: _____

Frekvens dagläckage: dagligen varje vecka mer sällan

gleskissare ≤ 3 mktioner /dag frequency ≥ 8 mktioner/dag nocturi normal

svag stråle lång, hård stråle krystning efterdropp lång mktionstid normal

Urinvägsinfektion som antibiotikabehandlats

Antal utan feber _____ Antal med feber (>38 grader) _____

Kommentar _____

Sexualanamnes

Erektion: Ja Nej Vet ej

Om erektion:

Rak penis vid erektion Ja Nej Vet ej

Penis kurverad nedåt vid erektion Ja Annan kurvering Nämligen _____

Utlösning: Ja Nej

Droppande, svår att få ut: Ja Nej Vet ej

Sexdebut: Ja Nej

Velat ha kvar förhuden om möjligt Ja Nej Vet ej

Nöjd med kosmetiken Ja Nej Vet ej

Kommentar _____

Fria kommentarer:

Undersökning utförd av: _____

datum _____

HOSE - Hypospadias Objective Scoring Evaluation

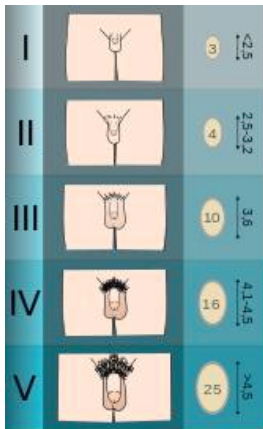
Assessor:

Patient:

Date:

Variable	Score	Diagram
1. Meatal location		
Distal glanular	4	
Proximal glanular	3	
Coronal	2	
Penile shaft	1	
2. Meatal Shape		
Vertical slit	2	
Circular	1	
3. Urinary Stream		
Single stream	2	
Spray	1	
4. Erection		
Straight	4	
Mild angulation (<math>< 10^\circ</math>)	3	
Moderate angulation (> 10° but <math>< 45^\circ</math>)	2	
Severe angulation (> 45°)	1	
5. Fimula		
None	4	
Single - subcoronal or more distal	3	
Single - proximal	2	
Multiple or complex	1	

Total



MANUAL för us vid prospektiv studie manlig DSD

Definiton av begrepp

Operationstyper:

Uretra: TIP =tubulariserad inciderad platta fritt transplanterat – kommentera vad vask lambå - kommentera om onlay eller tubulariserat graft 2seans

Upprättning: plissering ja/nej/vet ej -kommentera Nesbit eller Baskin inlay ventralt corpora – kommentera vilken graft

Penis undersöks med patienten liggande på britsen

Längden mäts mot höger pekfinger med fingerspetsen in dikt an mot symfyssen och i sträckt läge av penis och längden stämmer av mot fingret som jämförs med en linjal liggande på bordet. Mät gärna undersökarens finger innan!

Bredd mäts mitt på skaftet liksom omkrets, mäts med ett snöre och kontrollera måttet mot linjalen.

Kurvering i vila anges höftat i intervallet 0-10, 10-30, 30-60, 60-90 grader. Specialfall tipp av själva glans med rakt penis skaft.

Mått penislängd vid erektion efterfrågas. Mätes om möjligt vid undersökningen.

Mått på glans mäts med snöre och jämförs mot linjalen på bordet.

Bredd mäts på bredaste stället.

Vid 14 år viktigt fråga om glans är hård vid erektion av penis!

” Penis sedd från sidan” resp ” Penis sedd framifrån” ger utrymme att rita för att förtydliga till exempel kurvering eller ärrighet.

Meatus: Utseende på meatus om ej slitsformig.

Mått corona till meatus närmaste kant, mates med snore som ovan.

Mått meatus kant och ner till penoscrotalvinkeln, mates med snore som ovan.

Läge kryssas i men kan också läggas in i en eventuell skiss.

Ange om det finns en fistel, var den är belägen, enligt listan på meatus läge samt ange eventuellt hur stor mynningen är.

Preputiet: kan vara borttaget, opererat dvs klivet eller ihopsytt med en plastik dvs cirkulärt.

“**Tecken till BXO**” dvs vitaktig vävnad, här anges om det finns misstänkta områden men vi har inte krav på PAD-verifikation. Ange även var dessa förändringar finns och/ eller markera i skissen.

Testis palperas i liggande, ange storlek med hjälp av orchidometer.

Scrotum undersöks i stående, beskriv om scrotum är “normal” eller bifid. Kommentera om det finns annan patologi.

Graden av **penoscrotal transposition** uppskattas till mild eller svår partiell samt total efter hur mycket av scrotum som är belägen ovanför penisbasen.

Om tydliga **ärr** ses bör de beskrivas och ritas in på skissen och fotografierna bör tas så de syns.

Fotografi, 3 stycken tas från olika vinklar enligt CRF. De ska tas med digitalkamera med en tejbild med koden synlig på första bilden. De är inte avsedda att publiceras utan ska bara vara stöd för minnet och för utvärderingen. De bör tryckas ut snarast och bifogas CRF-formuläret.

2D och 4D: Försökspersonens hand kan kopieras i en vanlig kopiator. Mät dessutom 2:a och 4:e fingrets längd med skjutmått och skriv in i kopian. Bifoga kopian till CRF-formuläret. Räkna ut kvoten!

TANNERSTADIUM:

Könsorgan (man)

Tanner I

Förpubertal testiklarnas volym är mindre än 1,5 ml; penis längd är 3 cm eller mindre).

Tanner II

Testiklarnas volym är mellan 1,6 och 6 ml; skinnet på pungen blir tunnare, rodnar och förstoras; penis längd oförändrad.

Tanner III

Testiklarnas volym är mellan 6 och 12 ml; pungen växer ytterligare; penis börjar bli längre, runt 6 cm.

Tanner IV

Testiklarnas volym är mellan 12 och 20 ml; pungen växer ytterligare och mörknar; penis börjar bli längre, runt 10 cm och ökar i omkrets.

Tanner V

Testiklarnas volym är större än 20 ml; fullvuxen pung och penis omkring 15 cm i längd.

Könsbehåring (både man och kvinna)

Tanner I

Inget könshår alls (förpubertal nivå).

Tanner II

Liten mängd långa duniga hår och en något pigmenterad bas vid penis och pung (scrotum) hos män eller på de yttre blygdläpparna (labia majora) hos kvinnor.

Tanner III

Håret blir grövre och krulligt samt sprider ut sig.

Tanner IV

Vuxenlik hårkvalité, breder ut sig över blygdbenet (pubis) men endast sparsam behåring på låren.

Tanner V

Håret har också vandrat ut på låren

Questionnaire for follow-up of young men with hypospadias (translated to English by author)

General questions

1. What are your living conditions?

- I live with one parent
- I live with both parents
- I've moved out
- Other, please specify

2. Where do you live?

- In a major city (>200 000 inhabitants, e.g. Gothenburg)
- In a city (>40 000 inhabitants)
- In a village (15 000-40 000 inhabitants)
- In the countryside (<15 000 inhabitants)
- Don't know

3. Do you have any siblings?

- Yes, brother/s. _____
- Yes, sister/s. _____
- None.

4. Are you adopted?

- Yes
- No

5. Are your parents born in Sweden?

Yes

No, my mother is born in

No, my father is born in

6. What is your daytime activity?

Work

Studies

Unemployed

Other, please specify

7. What education do you have?

	Started	Finished
1st - 9th grade	<input type="checkbox"/>	<input type="checkbox"/>
10th-12th grade	<input type="checkbox"/>	<input type="checkbox"/>
University	<input type="checkbox"/>	<input type="checkbox"/>
Other _____	<input type="checkbox"/>	<input type="checkbox"/>

8. Did you receive any of the following forms of extra help in school?

Mark if one or more were correct

Specialized tutoring?

Tutoring in an adjusted, smaller group?

An extra instructor in school?

Other extra help in school?

9. If you know your birth weight and length, please submit as well as if you were born prematurely.

Birth weight in kg

Length at birth in cm

Born prematurely, number of weeks

10. Your present weight and height

Height in cm

Weight in kg

11. Your age

When were you born, year and month

How old are you now, years and months

Questions regarding hypospadias and operative treatment

12. How old were you when you received information from the Health Care regarding your hypospadias?

13. Do you remember what you found out?

14. Do you consider the information you received sufficient?

- Yes
- No
- Don't know

15. On a scale, can you mark how you perceived the information

1 2 3 4 5 6 7 8 9 10

Insufficient Sufficient

16. If you found the information insufficient, can you explain why?

17. Have you received information about your hypospadias from your parents?

- Yes
- No
- Don't know

18. If, yes, how old were you when you received the information?

19. Do you consider the information you received sufficient?

- Yes
- No
- Don't know

20. On a scale, can you mark how you perceived the information

1 2 3 4 5 6 7 8 9 10

Insufficient Sufficient

21. If you found the information insufficient, can you describe why?

22. How did you perceive the follow-up visits after your hypospadias surgery?

Mark on the scale what corresponds to your answer

1 2 3 4 5 6 7 8 9 10

Positive Negative

23. How did you perceive the information you received regarding your hypospadias surgery?

Mark on the scale what corresponds to your answer

1 2 3 4 5 6 7 8 9 10

Negative Positive

24. Do you have comments about the information you received regarding the surgery or the follow-up visits at your doctor?

25. How often do you think patients with hypospadias should come for doctors' appointments?

- Only once after surgery
- Three times in total (at 5 , 10 and 15 years of age)
- Every other year
- Yearly
- Don't know

26. What do you consider the optimal age for hypospadias surgery?

- < 1 year of age
- 1-3 years of age
- 4-7 years of age
- 8-11 years of age
- 12-15 years of age
- > 18 years of age
- Don't know

27. Have you received the support of a psychologist during up-bringing as a part of the hypospadias follow-up?

- No
- Yes
- Maybe
- Don't know

28. Would you have wanted psychological support during up-bringing as part of the hypospadias follow-up?

- No
- Yes
- Maybe
- Don't know

Questions about how hypospadias have affected you.

29. Has hypospadias affected you negatively during childhood (up until the age of 18)?

Mark on a scale from 1 - 10

1 2 3 4 5 6 7 8 9 10

No, not at all ○○○○○○○○○○ Yes, a lot

30. Has hypospadias affected your spare time (leisure activities) negatively?

1 2 3 4 5 6 7 8 9 10

No, not at all Yes, a lot

31. Has hypospadias affected your relations with friends negatively?

1 2 3 4 5 6 7 8 9 10

No, not at all Yes, a lot

32. Has hypospadias affected your relations with your parents negatively?

1 2 3 4 5 6 7 8 9 10

No, not at all Yes, a lot

33. Has hypospadias affected your relations with your siblings negatively?

1 2 3 4 5 6 7 8 9 10

No, not at all Yes, a lot

34. Has hypospadias affected your relations with partners negatively?

1 2 3 4 5 6 7 8 9 10

No, not at all Yes, a lot

Questions regarding puberty

35. When did you reach puberty?

(changed the pitch of your voice, had hair growth in armpits and on genitals, grew a lot in height)

- Much prior to my peers
- Just about the same age as my peers
- Much later than my peers

36. Do you consider hypospadias to have affected your puberty negatively?

- Yes
- No
- Don't know

37. How did it affect your puberty?

Questions on other illnesses and problems.

38. Have you ever attended Health Care for other medical problems?

- Yes
- No
- Don't know

39. If yes, where did you go?

- Hospital
- General Practitioner
- Youth Health Clinic
- Student's Health Clinic
- Other, please specify

40. Did you receive a diagnosis?

- Yes, I had

- No

41. Have you ever attended Health Care for psychiatric problems?

- Yes
- No
- Don't know

42. If yes, where did you go?

- School counsellor
- General Practitioners Office
- Youth Health Service
- Student's Health
- Psychiatric emergency
- Other, please specify

43. Did you receive a diagnosis?

- Yes, I had

- No

44. Have you ever considered seeking counselling (for example at a youth clinic for sexual and reproductive health) for questions regarding the appearance or function of your penis?

- Yes, and I have gone for counselling
- Yes, but I haven't gone for counselling
- No
- Don't know

45. Have you avoided seeking counselling at the youth clinic for sexual and reproductive health because of your hypospadias?

- Yes
- No
- Don't know

Question 46 - 67 are the PGWB instrument, not reprinted here.

Questions 68 - 69 are the BESAA instrument (16 statements), not reprinted here.

Questions regarding your penis

70. Have you had any of the following problems?

	Yes, now	Yes on one or two occasions	Yes, previously but not now	No	Don't know
Long voiding time	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Voiding difficulties (to start / to achieve a good urinary stream / takes long time to void)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Leakage	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urinary stream directed much downwards	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Urinary tract infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Fistulas (an extra hole where urine passes through)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Scarring	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

71. How pleased are you with the following?

	Very pleased	Pleased	Displeased	Very displeased
The length of your penis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The direction of your penis upon erection	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The sensibility on glans	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

+ The 4 PPS / PPPS statements not reprinted here

73. Are you circumcised?

- Yes
- No
- Don't know

74. If you are circumcised, would you have preferred not to be?

- Yes
- No
- Don't know

75. If you have measured your penis, what length did you measure?

- | | 1-5 cm | 6-9 cm | 10-12 cm | 13-15 cm | >16 cm | Don't know |
|-------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| During erection (hard) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| Not during erection (flaccid) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

76. Did your penis grow during puberty?

Mark on the scale what corresponds to your opinion

1 2 3 4 5 6 7 8 9 10

No, not at all Yes, a lot

77. Comments about how you think your penis changed during puberty:

Questions regarding glans

Sometimes the sensation on glans is affected after surgery, which is why we will ask the following questions.

78. How do you consider the size of your glans?

- Just the right size
- Too big
- Too wide
- Too small
- Don't know

84. Can you get an orgasm from touching /fondling

Touching / fondling could be both by yourself or your partner

- Yes
- No
- Don't know

85. Have you had an ejaculation during orgasm?

- Yes
- No
- Don't know

86 Are you interested in physical contact with your partner?

"Physical contact" refers to actions such as kissing, hugging, cuttling, fondling or sexual intercourse

- Yes
- No
- Don't know

87. How many times during the last month have you masturbated?

- Not at all
- Occasionally
- 1-2 times/week
- Every day
- Don't know

88. Has hypospadias affected your sexual experiences negatively?

- Yes
- No
- Don't know

89. If hypospadias has affected your love life, can you describe how?

90. Have you had sex with anyone?

(had sex with a partner)

- Yes
- No
- Don't know

Questions about sex

(these questions are only answered if affirmative answer in the previous question)

91. Can you have intercourse with penetration?

- Yes
- No
- Don't know

92. How old were you when you had intercourse with penetration for the first time?

93. Do you experience pain during intercourse?

- Yes
- No
- Don't know

94. Can you get an orgasm during intercourse?

- Yes
- No
- Don't know

95. If you cannot get an orgasm, do you have an opinion on why?

96. Are you satisfied with your sexual experiences?

- Yes, very
- Yes, quite
- No, not particularly
- No, not at all

97. How often do you have intercourse?

- Never
- < once / month
- 1-2 times / month
- 1-2 times / week
- Every day
- Don't know

98. How often would you like to have intercourse?

- Never
- < once / month
- 1-2 times / month
- 1-2 times / week
- Every day
- Don't know

99. Do you presently have a partner?

- Yes
- No
- Don't know

100. Who will usually initiate sex?

- Me
- My partner
- Both of us equally often
- I don't have a partner
- Don't know

101. Can you and your partner talk about your love life?

- Yes
- No
- Don't know

102. How would you describe your ability to enjoy sex?

- Always satisfying
- Sometimes satisfying
- Seldom satisfying
- Never satisfying
- Don't know

This question is about sexual orientation

103. Mark the statement that most correctly describes you

	Only heterosexual	Mainly, but not only heterosexual	As much heterosexual as homosexual	Mainly, but not only homosexual	Only homosexual
During the last 12 months, my sexual behavior has been	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
During the last 12 months, my sexual fantasies and desires have been	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
During my life, my sexual behavior has been	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
During my life, my sexual fantasies and desires have been	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Questions regarding gender identity

104. During the last 12 months, have you been satisfied with being a man?

- Always
- Often
- Sometimes
- Seldom
- Never

105. During the last 12 months have you ever felt unsure of your gender identity, i.e. felt somewhere between man and woman?

- Always
- Often
- Sometimes
- Seldom
- Never

106. Are you in need of counselling from a psychologist /sexologist?

- Yes
- No
- Don't know

107. Have you ever been in need of counselling regarding sexual questions?

- Yes
- No
- Don't know

Other questions

108. Have you received help filling in this questionnaire?

- Yes
- No

THANK YOU for participating!

If there is anything else you would like to tell us, please use the field below.
