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LONG-TERM PERSPECTIVES ON HYPOSPADIAS

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Long-term perspectives on hypospadias

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Stockholm 2016

“To live is to choose. But to choose well, you must know who you are and what you stand for, where you want to go and why you want to get there.”

-Kofi Annan

To my family.

ABSTRACT

Hypospadias, a multifactorial condition and one of the most common congenital malformations, has an incidence of 1/125 boys born. The infants are born with an ectopic meatus placed ventrally on the penis varying from a glanular to a perineal position, a cleaved prepuce, and often a penile curvature. The treatment is surgical and aims to achieve a satisfactory cosmetic result, an ability to void normally, and to have satisfactory sexual functions.

The aim of this thesis was to evaluate the long-term outcome of men born with hypospadias. All the studies were based on a questionnaire sent to 167 patients and 169 age-matched controls, as well as 47 circumcised controls operated for phimosis. A subgroup of patients and controls came for a clinical exam, which included uroflowmetry and a psychiatric screening.

Study I, investigating the *urological outcome and cosmetic result after surgery*, revealed that patients had more voiding dysfunction and a lower maximal urinary flow rate. They also had a shorter penile length and were less satisfied with the cosmetic appearance than controls. Patients with proximal hypospadias had a shorter penile length and were less satisfied than the other patients.

Study II, focusing on the *psychosocial long-term outcome,* revealed that patients with hypospadias have a comparable psychosocial situation to controls and a good quality of life. Patients with proximal hypospadias had a history of more medical follow-up and psychological support than patients with more distal hypospadias and also expressed a need for more psychological support in the future.

The aim of *Study III* was to investigate the *fertility and psychosexual function*. A comparable fertility and a favourable psychosexual function were revealed, with 80% of both patients and controls expressing satisfaction with their sexual life. Patients with proximal hypospadias had a lower reported fertility compared with controls and with patients with more distal hypospadias. Proximal hypospadias decreased the odds of a man being satisfied with his sexual life.

Study IV assessed the *prevalence of psychiatric symptoms* of ADHD, affective disorders and other common psychiatric diagnoses. The results did not identify an increased psychiatric morbidity in men with hypospadias.

In conclusion, the long-term outcome in men born with hypospadias is, in general, good. However, genital appraisal is impaired in all groups with a risk of causing both psychosocial and psychosexual impairment. Patients with proximal hypospadias need more follow-up and support, and transitional care is important.

SVENSK SAMMANFATTNING

Hypospadi är en av de vanligaste medfödda missbildningarna och drabbar 1 av 125 födda pojkar. Det är en multifaktoriell sjukdom, vilket innebär att den orsakas av både genetiska faktorer och miljöfaktorer. Hypospadi innebär att en pojke föds med urinrörsmynningen på undersidan av penis. Beroende på när under urinrörsutvecklingen missbildningen uppstår kan urinrörsmynningen vara belägen allt från ollonets spets och ner till under pungen. Penis är också ofta krokig och förhuden kluven. Behandlingen är kirurgisk och operationen sker oftast vid 9-18 månaders ålder. Målet med operationen är att få urinrörsmynningen att hamna på ollonets topp, att få penis rak och se till att pojken kan kissa bra. Ett bra kosmetiskt resultat och att kunna ha sex i framtiden är också viktiga mål med behandlingen.

Denna avhandling syftar till att ta reda på hur dessa patienter mår när de blivit vuxna, och hur deras medfödda hypospadi har påverkat deras liv i olika avseenden. 167 patienter med hypospadi med en medelålder på 34 år och 169 kontrollpersoner utan hypospadi med motsvarande ålder deltog i studien. Ytterligare en kontrollgrupp bestod av patienter som blivit omskurna i barndomen på grund av för trång förhud. En enkätstudie med en web-baserad enkät med drygt 300 frågor har genomförts och patienter och kontrollpersoner har undersökts på mottagningen. På mottagningen genomgick de även en psykiatrisk screeningundersökning.

I **studie I** har urologiska och kosmetiska aspekter hos patienterna med hypospadi undersökts. Undersökningen visade att de hade mer urinvägsbesvär och att de var mindre nöjda med utseendet av penis än personerna i kontrollgruppen. De hade också en kortare penis jämfört med männen i kontrollgruppen och detta var relaterat till svårighetsgraden av hypospadi. Patienterna med en svårare form av hypospadi, då urinrörsmynningen är närmare pungen, var mindre nöjda med utseendet och hade en kortare penis än övriga patienter och kontrollpersoner.

I **studie II** studerades om hypospadin hade haft en påverkan på patienternas sociala situation, såsom jobb, familj och fritidsintressen. Livskvaliteten hos patienten och hur de knyter an till andra människor undersöktes. Resultaten visar att de lever i en motsvarande social situation som kontrollgruppen och att de har en god livskvalitet. Männen med en svårare form av hypospadi har varit i behov av, och önskar även i framtiden, både urologisk och psykologisk uppföljning i större utsträckning än övriga patienter.

Studie III undersökte om patienterna med hypospadi hade en påverkad fertilitet och sexuell funktion. Studien visade att patienter och kontrollpersoner i samma utsträckning hade gjort en kvinna gravid någon gång (rapporterad fertilitet), men den svårare patientgruppen hade färre barn och en lägre rapporterad fertilitet. Hypospadipatienter som blivit omskurna i samband med operation och omskurna kontrollpersoner hade en lägre känsel på ollonet än icke omskurna kontrollpersoner. Den sexuella funktionen var god, de hade en motsvarande ålder vid sexdebut, och motsvarande antal sexpartners.

Åttio procent av patienter och kontrollpersoner var nöjda med sitt sexliv. Att vara nöjd med utseendet av penis ökade sannolikheten för att vara nöjd med sitt sexliv hos patienter, men inte hos kontrollgruppen. Att ha en svår hypospadi minskade oddsen för att vara nöjd med sitt sexliv.

Studie IV undersökte förekomsten av psykiatriska symptom talande för t.ex. ADHD, ångestsjukdomar och andra psykiatriska diagnoser. Studien visade inte någon ökad förekomst av psykiatriska symptom hos patienter jämfört med kontrollgruppen.

Sammanfattningsvis talar resultaten av studierna för att patienter som fötts med hypospadi mår bra i allmänhet. De har lika goda chanser att leva ett liv med jobb, familj och barn i motsvarande grad som andra, ha en god sexuell funktion och har ingen ökad förekomst av psykiatrisk sjuklighet. Många är missnöjda med utseendet av penis efter operation och detta kan medföra konsekvenser på uppväxten i stort och på sexlivet. En fortsatt utveckling av kirurgisk teknik är viktig liksom stöd till dessa patienter under uppväxten och under livet. Den grupp med patienter som hade en svårare form av hypospadi uppvisade mer problem och var mindre nöjda. Resultaten av studierna talar för att de behöver en utökad uppföljning med mer stöd, både urologiskt och psykologiskt. Det är därför viktigt att de förs över till en vuxenurolog med kunskap om hypospadi och dess omhändertagande samt andra specialister vid behov när de inte längre kan följas av barnsjukvården.

PREFACE

Milan Brodsky was a paediatric surgeon and urologist who was interested and invested in individuals with hypospadias unto the end of his life. He performed a meticulous work of putting together a large body of material with all the patients he had met, which became the base of this thesis. After his retirement, he left all his data to my supervisor, Agneta Nordenskjöld, with the hope that she would take care of it. She gave me the honour of working with it, and here we are now, with a thesis. I hope Milan would have been happy with the result of the work performed based on his material.

I feel grateful to have had the possibility to meet with all these patients during my work, in person at the outpatient clinic or trough questionnaires, and for them sharing with me a part of their lives and their experience of living with hypospadias. My hopes are that this thesis will help to improve the healthcare for these patients with hypospadias and to make their experience of being born with hypospadias a better one.

Astrid Lindgrens Barnsjukhus, November 1st, 2016.

Lisa Örtqvist

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles and manuscripts. The papers will be referred to in the text by their Roman numerals (*I-IV*).

I. **Örtqvist L**, Fossum M, Andersson M, Nordenström A, Frisén L, Holmdahl G, Nordenskjöld A
Long-term followup of men born with hypospadias: urological and cosmetic results
The Journal of Urology 2015 Mar;Vol. 193, 975-982

II. **Örtqvist L**, Andersson M, Strandqvist A, Nordenström A, Frisén L, Holmdahl G, Nordenskjöld A
Psychosocial outcome in adult men born with hypospadias
The Journal of Pediatric Urology, DOI information: 10.1016/j.jpurol.2016.08.008.

III. **Örtqvist L**, Fossum M, Andersson M, Nordenström A, Frisén L, Holmdahl G, Nordenskjöld A
Sexuality and fertility in men with hypospadias, improved outcome
Accepted in Andrology

IV. **Örtqvist L**, Engberg H, Strandqvist A, Nordenström A, Holmdahl G, Nordenskjöld A, Frisén L
No increase in psychiatric symptoms in men with hypospadias
Submitted

LIST OF ABBREVIATIONS

A.D.	Anno Domini (After Christ)
ADHD	Attention-deficit/hyperactivity disorder
AIS	Androgen insensitivity syndrome
AMH	Anti-müllerian hormone
ASD	Autism spectrum disorders
ASRS	Adult ADHD self-report scale
BES	Body esteem scale
CAIS	Complete androgen insensitivity syndrome
CAH	Congenital adrenal hyperplasia
CPRS-S-A	Comprehensive psychopathological rating scale- self-rating scale for affective syndromes
CRF	Case report form
DISF-SR	Derogatis interview for sexual functioning
DHT	Dihydrotestosterone
EDC	Endocrine disruptimg chemicals
HAGD	Hypospadias associated with other genital disorders
IH	Isolated hypospadias
IVF	In vitro fertilisation
LS	Lichen sclerosus (former BXO)
LUTS	Lower urinary tract symptoms
MINI	Mini international neuropsychiatric interview
OR	Odds ratio
PAIS	Partial androgen insensitivity disorder
PGWBI	Psychological general well-being index
PPS	Penile perception score
QoL	Quality of life

RQ	Relationship questionnaire
SPR	Swedish population register
SRY	Sex determining region Y
TDS	Testicular dysgenesis syndrome
VAS	Visual analogue scale
WHO	World health organisation

CONTENTS

LIST OF DEFINITIONS

Androgens
A steroid hormone that activates or controls the development and maintenance of male sex characteristics.

Penile curvature
An abnormal down-ward bend in the penis observed at erection.

Confidence interval
The probability that a population parameter will fall between two set values.

Disorder of sex development
Congenital conditions where development of chromosomal, gonadal or anatomical sex is atypical.

Fertility
The capacity to conceive or to induce conception.

Genotype
The genotype is an individuals genetic characteristics, the genome.

Gonads
The gonads or sex glands are the endocrine glands that produces the gametes (sex cells) of an organisms. In males the gonads are called testes, and in females ovaries.

Hypospadias
Congenital genital malformation with the urethral opening located on the ventral side of the penis or scrotum.

Likert Scale
Bipolar ranking scale, frequently used in questionnaires, with the two ends of the scale representing opposite positions of the opinion.

Odds ratio
The ratio of the odds of an event occurring in one group to the odds of the event occurring in another group. A measure of association between an exposure and an outcome.

Phenotype
An individual's expressed physical traits.

Phimosis
A condition of the penis where the foreskin cannot be fully retracted over the glans penis, which sometimes needs surgical treatment with circumcion or preutial plasty.

Quality of life
A broad multidimensional concept including an individuals subjective evaluation of both positive and negative aspects of life combining a person's life conditions and satisfaction.

THESIS AT A GLANCE

Paper	AIM	METHOD/ DESIGN	RESULTS	CONCLUSION
I	To evaluate the surgical, cosmetic and urological results after hypospadias surgery.	Cross-sectional follow-up study with 167 adult men with hypospadias and 169 age-matched and 47 circumcised controls. All participants completed a questionnaire assessing satisfaction with cosmetic results, body-esteem and LUTS. 47 patients and 49 controls came for a clinical examination.	Patients were less satisfied with the penile cosmetic outcome than controls, and the satisfaction was even lower in patients with more proximal hypospadias. Penile length was shorter in patients than controls, and they had more voiding dysfunction symptoms as well as a lower maximum lower urinary flow rate.	The satisfaction with the cosmetic results is lower in patients. They present with more voiding symptoms and a shorter penile length. Patients with proximal hypospadias are more affected than those with more distal hypospadias.
II	To evaluate the long-term psychosocial outcome after hypospadias surgery.	Same design as above, but the circumcised controls were excluded. Psychosocial data, HRQoL and attachment styles were assessed with a questionnaire.	Patients and controls had a comparable level of quality of life. They had a partner and children, and worked to the same extent. Patients had a lower level of education and lived more at home with their parents than controls. Patients with proximal hypospadias were shorter than controls and expressed a larger need of follow-up compared with more distal cases.	Patients treated for hypospadias have a good quality of life, and can be expected to have a normal psychosocial life, have a partner and children to the same extent as the general population.
III	To evaluate psychosexual function, assess fertility and gender-related development in men born with hypospadias.	Idem as in *Study I*, both control groups included. All participants responded to a questionnaire assessing psychosexual functioning, gender related development and fertility.	There were no differences in having a partner, reported fertility, age at sexarche or number of sex partners between patients and controls. In patients, the odds of being satisfied with their sexual life were higher, with a higher cosmetic satisfaction. Penile length had no association with sexual satisfaction. Gender related development was comparable. Patients with proximal hypospadias had a lower reported fertility, were less satisfied with their sexual life and more frequently reported anejaculation.	Psychosexual long-term outcome is satisfactory and fertility is comparable. Satisfaction with genital appearance is important. Patients with proximal hypospadias have more problems, both with sexual function and fertility.
IV	To evaluate if men born with hypospadias have more psychiatric problems than controls.	Idem as in *Study I*. 167 patients and 169 controls answered a questionnaire assessing symptoms of ADHD and affective syndromes. Thirty-three patients and 47 controls underwent a short psychiatric screening at the outpatient clinic.	21% of both patients and controls reported current or previous psychiatric symptoms. There were no signs of an increased prevalence of symptoms of ADHD among patients, nor symptoms of an affective syndrome.	An increased psychiatric morbidity in men with hypospadias cannot be supported by this study.

1 INTRODUCTION

Hypospadias is a congenital malformation characterized by an ectopically placed meatus on the ventral side of the penis or scrotum, a cleaved foreskin and sometimes a penile curvature[1]. It is a multifactorial disease, caused by both genetic and environmental factors[2]. The birth prevalence is 1/125 boys born, which is why hypospadias is one of the most common congenital malformations[3]. Treatment consists of surgery to achieve a cosmetically normally looking penis with the meatus located on the tip of the glans without curvature, and with a future normal sexual function.

With the aim of introducing the subject of hypospadias, a background containing a short historical view, epidemiology, aetiology, normal and abnormal sex development as well as clinical features, management and outcome measures of hypospadias will follow.

1.1 HISTORICAL ASPECTS OF HYPOSPADIAS

Hypospadias is a term derived from Greek and consists of "hypo" which means under and "spadon" which means rent or a fissure. Galen (130-199 A.D.), the physician to the Gladiators in Rome was the first to mention the term "hypospadias" (**Figure 1**)[4].

Figure 1. Galen, physician of the gladiators.

Galen's anatomical knowledge was limited, since autopsies were forbidden, but European medicine was dominated by his theories for 1,500 years. Galen wrote about the difficulties caused by penile curvature, at that time called chordee, during intercourse and difficulties for the sperm reaching the uterus, presenting a fertility problem, which could be solved by dividing the frenulum. During this period other physicians also described "amputation of the glans beyond the orifice" as the solution to bring the neo-meatus to the tip and centre of

the glans[1,5]. A thousand years later, in 1556, the next scientific developmental step was taken when a boy with penoscrotal hypospadias was treated by Amatus Lusitanus, with a canal being created from the proximal ectopic urinary meatus up to the penile shaft. From here on advances in anatomical knowledge concerning the pathology of hypospadias and surgical techniques for both neo-urethral creation and chordee correction were made, and from the middle of the nineteenth century several different repair techniques were developed. The techniques used today derive from this period and its innovative surgeons and over 300 surgical techniques have been described[1,4].

There have probably been a large number of famous individuals with hypospadias throughout history who have not left any specific historical footprints related to their condition. King Henry II of France was not one of them, however. He married Catherine de Medici in 1533 when they were both 14 years old, to strengthen the ties between France and Italy. He had a severe chordee and despite an active sexual life, after 10 years of marriage they still had no children. However, after a successful correction of his chordee, he fathered 10 children with his wife[4].

1.2 EPIDEMIOLOGY

Earlier studies from especially Europe and the USA report a prevalence up to a maximum of 3 per 1,000 births, with 2/3 to 3/4 being distal hypospadias[1]. This prevalence has, however, been increasing over the last decades[3,6,7]. A Swedish study has recently shown an increase in prevalence from 4.48 to 7.85 per 1,000 live-born boys from 1990 to 1999, and from 6.05 to 7.97 per 1,000 between 2000 and 2009[3]. The increase included both distal and proximal cases, and could not be explained by known risk factors[3]. The explanation for this increase in prevalence remains unclear, but factors such as improved surgical techniques leading to better fertility, more gene-environment interactions as well as different data collection methods could be part of the explanation. The increase has however been reported in a number of different regions/countries, using different data collection methods and the increase in prevalence has also occurred in other possibly aetiologically related conditions, supporting these data.

Apart from having an affected relative, low birth weight is the main risk factor for hypospadias[3]. Associated risk factors are a small placenta and being born small for gestational age[8,9]. Other reported risk factors are, for example, a diet without meat and fish and in vitro fertilisation (IVF), but these results are varying[10,11]. The above mentioned Swedish study confirmed that low birth weight for gestational age, IVF, a high maternal BMI and being born as a twin or being born by parents from Asia or Europe (Nordic countries excluded) increased the risk for hypospadias[3].

1.3 AETIOLOGY

Hypospadias is a multifactorial disease caused by both environmental and genetic factors. In most cases, the cause for each individual, however, remains unknown. Genetic causes are probably more important in proximal variants, whereas other factors, such as preterm delivery and being small for gestational age (SGA) are more probable causes in distal cases. This aetiological heterogeneity could be a result of different embryonic processes at different points of time during development[12].

Genetic factors

The fact that familial clustering is seen in up to 25% of cases of hypospadias, strongly suggests that genetic factors are involved in the pathogenesis. Today, a cause can be identified in approximately 20% of all cases, most often in patients with proximal hypospadias[13]. The presence of a relative with hypospadias is the main risk factor and the recurrence risk increases with the severity of the hypospadias[8]. A large number of mutations have been found in candidate genes in populations with hypospadias, even if most mutations have only been described once and the function of the mutations remains unknown in most cases. A majority of the identified mutations were found in individuals with more proximal hypospadias suggesting that proximal hypospadias have a more monogenic or polygenic aetiology and distal hypospadias a more multifactorial etiology[2]. Obvious candidate genes for hypospadias are genes involved in the development of the male external genitalia, and mutations have been found in more than 60 genes involved in genital development. Such genes are, for example, *WT1* (*Wilms Tumor 1)*, *SF1* (*NR5A1 or Steroidogenic factor 1*) and *FSHR (Follicle Stimulating Hormone Receptor)* which are involved in the development of the internal genitalia and *LHCGR* (Luteinizing Hormone/ Choriogonadotropin Receptor*)*, a gene responsible for later parts of the development. Especially important are the androgen receptor gene (AR) and genes for the enzymes in the process converting cholesterol to testosterone (e.g. 17*β-HSD (17beta hydroxy steroid dehydrogenase))* and testosterone to dihydrotestosterone (DHT), *SRD5A2* (5alfa reductase)[14,15].

Environmental factors

Hypospadias has been included as a part of the Testicular dysgenesis syndrome (TDS), discussing a common aetiology of cryptorchidism, testicular cancer, male infertility and hypospadias[1]. The hypospadias part of this syndrome is, however, questioned as will be further discussed in the chapter on fertility. Several studies have investigated the theory of endocrine-disrupting chemicals (EDC), suggesting that the chemicals in our environment could disturb the endocrine system in a number of ways. In the case of hypospadias, an antiandrogen mechanism is suggested. It still remains unclear whether the levels of EDC in our environment could really cause disturbances in sex development[16]. The use of oral contraceptives during a part of the pregnancy results in oestrogen exposure, but no strong evidence has been found for this correlation[2].

1.4 SEX DEVELOPMENT

Sex can be defined at three different levels. The X and Y- chromosomes determine the *chromosomal sex*, or genetic sex. *Gonadal sex* is determined by the kind of gonadal tissue present, testes or ovaries. The *phenotypic sex* consists of the internal and external genitalia, expression of secondary sex characteristics and behaviour (**Figure 2**).

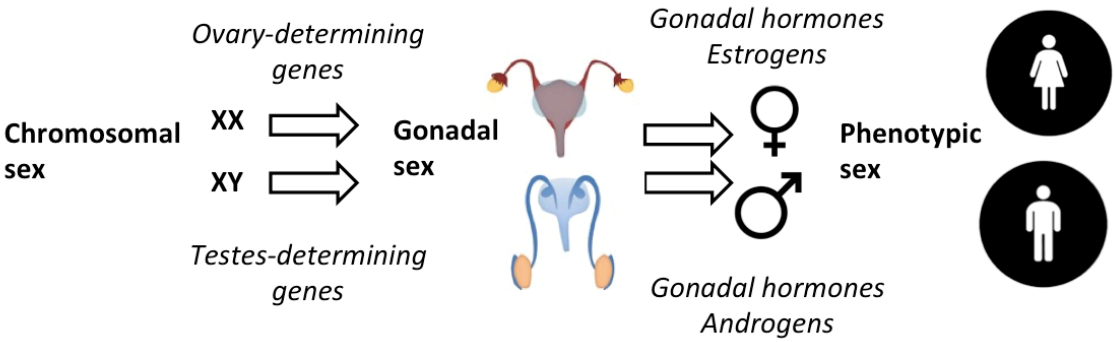

Figure 2. Chromosomal, gonadal and phenotypic sex.

Normal sex development

The embryo has undifferentiated genitalia, with the possibility to become female or male, until the 6th week of embryonic life. The gonads are bipotential initially and can form either testes or ovaries. In the typical situation, genetic sex, as determined by the chromosomal constitution, decides whether the gonads should develop into testicles or ovaries[17]. The Y chromosome contains the sex-determining region (SRY). The protein product of this gene is a transcription factor initiating a cascade of downstream genes directing the bipotential gonads to become testes in males (**Figure 3**).

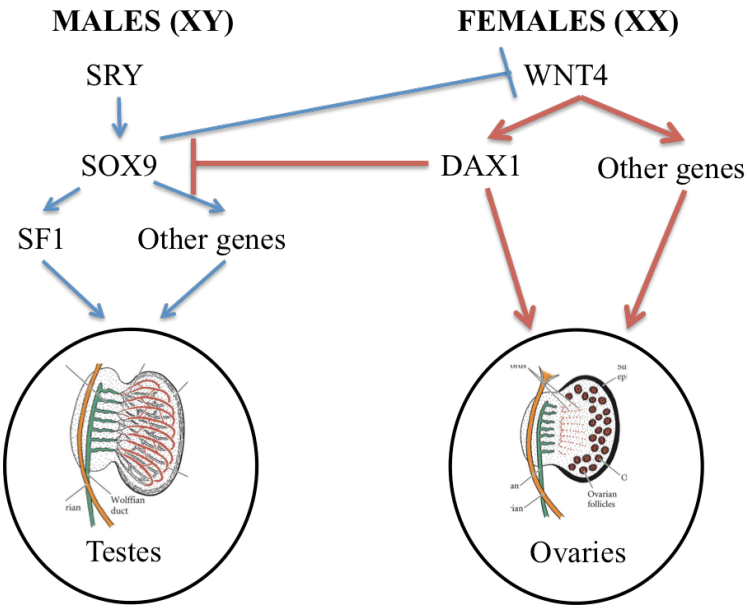

Figure 3. Genes responsible for sex determination.

As with many other developmental processes, the sex development process is sensitive to gene dosage effects, and duplications and deletions in the human genome are associated with disorders of sex development (DSD)[18]. The molecular regulation of the differentiation of the testes depends on the gene *SOX-9* (*SRY-box 9)*, which is up-regulated by SRY. *SOX-9* activates in its turn *SF-1* and other genes responsible for testis differentiation, and inhibits at the same time *WNT4* (*WNT family member 4)*, the gene inducing ovary differentiation. In females, with *WNT4* staying uninhibited, the gene *DAX1 (nuclear receptor subfamily 0 group B member 1)* is up-regulated, which inhibits *SOX9* and other genes, and induces ovarian differentiation. In the absence of SRY and the presence of two X chromosomes, ovaries develop[19].

One X chromosome is necessary in all human beings; two are needed to develop ovaries, and not more than one X chromosome to develop testicles. Simplified, one can say that the development of male internal and external genitalia will occur in the presence of specific testicular hormones, or female genitalia in its absence (**Figure 4**).

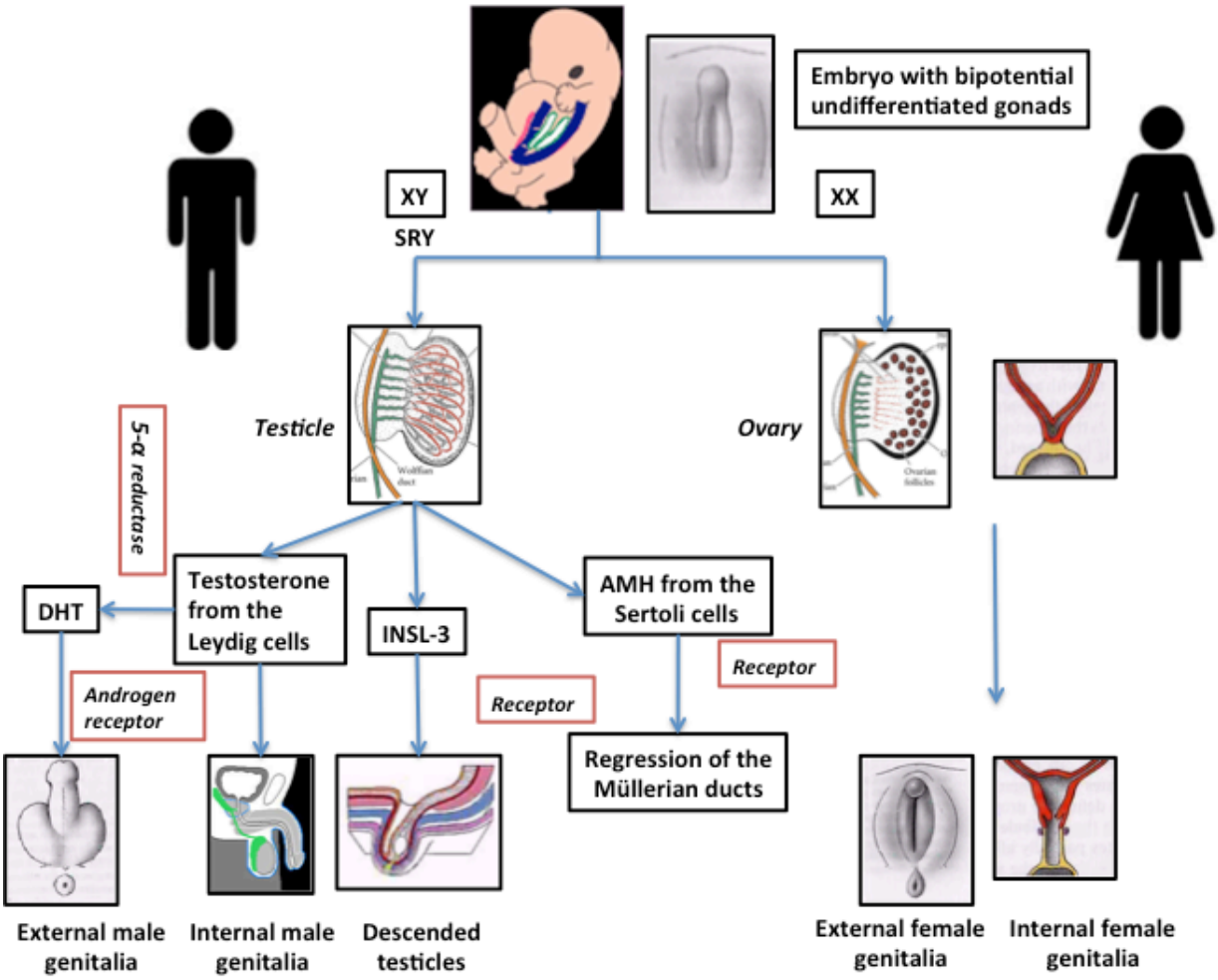

Figure 4. Normal sex development.

Internal genitalia are developed from the Wolffian ducts in males and from the Müllerian ducts in females, while the external genitalia are developed from the same structures for both males and females.

The testicles produce hormones required for a normal male genital development. Testosterone is produced by the Leydig cells, and is partly converted to DHT by 5α-reductase in the genital skin and the urogenital sinus. Testosterone stimulates the development of the male internal genitalia from the Wolffian ducts and DHT (10 times more potent than testosterone) is necessary for the development of the external male genitalia. The Sertoli cells produce Anti-müllerian hormone (AMH). AMH induces the regression of the Müllerian ducts[20]. The testicles also produce INSL-3, a hormone which mediates intra-abdominal testicular descent[17]. The development of female internal and external genital organs is induced by oestrogens produced by the ovaries and from maternal and placental sources[21].

The external genitalia are derived from the same cloacal folds in both males and females, located around the cloacal membrane, and look identical until the end of the 6th week. The cloacal folds join cranially to form the genital tubercle, while they are subdivided caudally into the urethral folds and the anal folds. At the same time, the genital swellings, another pair of elevations, become visible, and will become the scrotal swellings in the male and the labia majora in the female. In the male development, androgens drive the process, which includes elongation of the genital tubercle into the phallus. The urethral folds follow the elongation and form the urethral groove up to the beginning of glans. The urethral plate is formed by the urethral groove covered with an epithelial lining. The urethral folds cover the urethral plate, creating the penile urethra at the end of the third month. The most distal part of the urethra, including meatus, is created later, during the fourth month. It is thought that ectodermal cells from the tip of the glans migrate inwards to form a short epithelial cord, and a lumen is created. The scrotal swellings move downwards, and are separated by a septum, creating the scrotum. The female external organs are formed by the genital tubercle forming the clitoris, the urethral folds developing into labia minora, and the genital swellings into labia majora[21].

Disorders of male sex development (Male DSD)

DSD is an umbrella term defined as congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical[22]. The pathology of DSD can be located at three levels; a) problems with the development of the gonads, b) dysfunction of the gonads or c) defects in the target organs[18]. Individuals with DSD vary in phenotype concerning the genital phenotype from completely female genitalia to male-appearing genitalia. The degree of virilisation depends on the levels of androgens, and the responsiveness to the androgens (**Figure 5**). The diagnosis is often made at birth, but individuals may be undiagnosed until puberty or later. According to the new nomenclature and classification, DSD is divided into sex chromosome DSD (e.g. 47, XXY, Klinefelter

syndrome), 46, XY DSD (e.g. CAIS) and 46, XX DSD (as disorders of gonadal development)[22]. This chapter will focus on the XY DSD diagnoses that are seen in combination with hypospadias, presented in order from high to low prevalence.

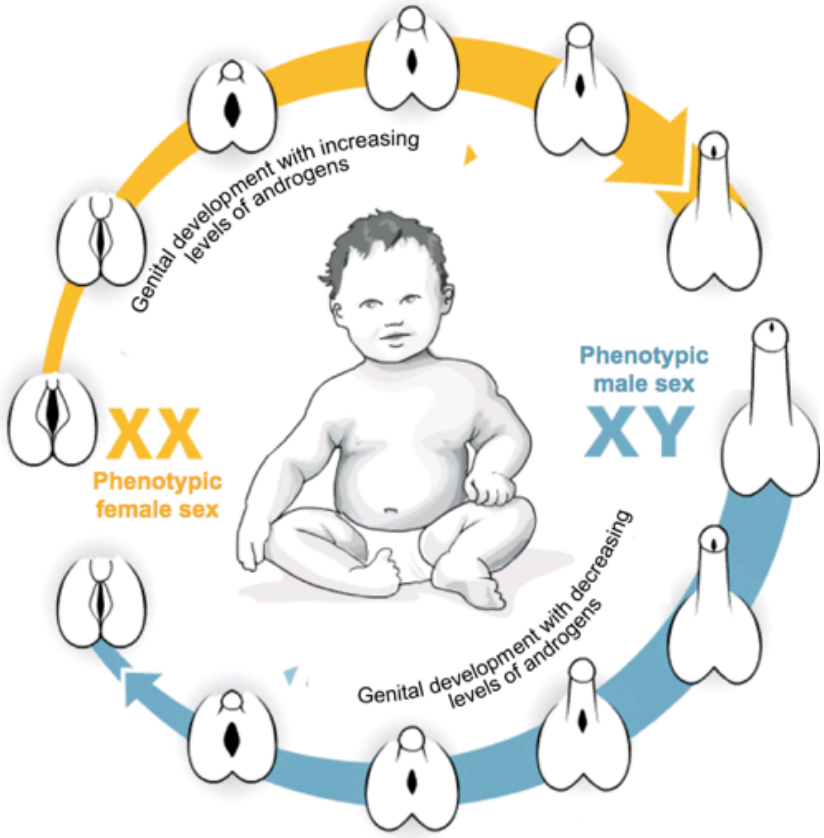

Figure 5. Genital development depending on testosterone levels. Grafik: Johan Andersson, DN. Published with kind permission of Dagens Nyheter.

Complete insensitivity to androgens (*Complete Androgen Insensitivity Syndrome*, *CAIS*) is a form of DSD that depends on either a loss in number, loss of binding affinity, or loss of function of the androgen receptors[18]. It is caused by inactivating mutations in the gene for the androgen receptor (*AR*), located on the X-chromosome. A partial insensitivity, PAIS, causes an incomplete masculinization with, for example, hypospadias, cryptorchidism or infertility. The condition is X-bound recessive, which means that 46, XX individuals are carriers and 46, XY individuals are affected. The recurrence risk for a woman who is a carrier to have an affected child is 50% if the child has a 46, XY karyotype.

17β-hydroxysteroid dehydrogenase is involved in the conversion from androstenedione to testosterone. A *deficiency in 17β-hydroxysteroid dehydrogenase* in 46, XY individuals usually results in normal male Wolffian duct structures and under-masculinized external genitalia but may also present as severe hypospadias. If the diagnosis is not set at birth, these individuals are usually raised as females. Due to a rise in serum testosterone, which is produced in the testes at the time of puberty, virilisation however occurs during puberty. A *lack of 5α-reductase*, an enzyme needed to convert testosterone to DHT, affects the development of external genitalia with phenotypes varying from female external genitalia to a small phallus and hypospadias, depending whether there is a total or partial enzyme deficiency[23]. Due to an isoenzyme produced in skin and liver, further virilisation can occur

if the gonads are left, which can then produce testosterone at puberty. The testosterone is converted to DHT with virilising effect both psychologically and on external genitalia[24].

Partial gonadal dysgenesis, when the gonads are partially dysfunctional is caused by an abnormal gonadal morphogenesis or differentiation in early foetal life. Depending on the degree of dysfunction, the baby presents with varying degrees of undermasculinisation[18,24].

Ovotesticular DSD is a specific form of gonadal dysgenesis, with both ovarian and testicular tissue present in either the same gonad or in contralateral gonads in the individual. The clinical presentation depends on the amount of testis tissue producing testosterone, with varying degrees of virilisation.

1.5 CLINICAL FEATURES OF HYPOSPADIAS

The anatomy of hypospadias

Except for three different features on the ventral side, the anatomy of the hypospadiac penis is similar to the normal penis. These features consist of: 1) an ectopic urethral orifice, 2) an abnormal foreskin and 3) a penile curvature (**Figure 6**).

Figure 6. *A penoscrotal hypospadias with a split prepuce and a penile curvature. The pen indicates the urethral plate.* Surgery Illustrated – Surgical Atlas Two-stage hypospadias repair with inner preputial layer Wolfe graft (Aivar Bracka repair) Silvio Altarac et al. 2012 BJU INTERNATIONAL | 110, 460–473. Published with kind permission of John Wiley and Sons.

An arrest in development results in an abnormal ventral coverage of the midline perineal mesenchyme over the urethral plate during the canalization, resulting in the *ectopic urethral* opening[1]. The urethral opening is most commonly arrested close to or near the coronal groove of the glans. The arrest occurs in that case during the 14th or 15th week of development. The later the arrest of the normal development occurs, the more distal the hypospadias (**Figure 7**).

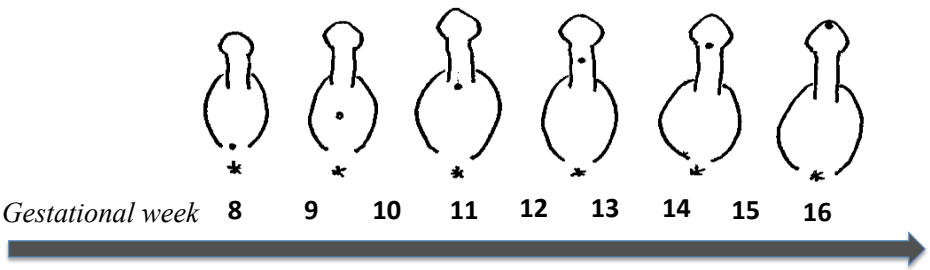

Figure 7. Meatal placement at different times of the genital development.

An early arrest in development stops the fusion of the outer genital folds resulting in two hemiscrota[1]. The *cleaved prepuce* or abnormal foreskin is also a consequence of the arrest in the urethral development. At eight weeks of gestation the preputial folds appear on both sides of the penile shaft and join dorsally of the penis. Because of the incomplete development of the urethra, the preputial folds cannot encircle on the ventral side. The consequence is an absent prepuce on the ventral side, and an excessive preputial tissue dorsally[25]. The median raphe of the phallus also develops abnormally. A deficiency of the mesenchymal growth may lead to a zig-zag shaped raphe ending which splits into two branches, one on each side distally to the "dog-ears" or corners of the split prepuce. The triangular area between the two branches lacks Buck's fascia and subcutaneous tissue, which is an important aspect during surgery[1]. *The penile curvature*, the abnormal bend in the penis observed on erection, is present in many patients with hypospadias, but is more common and severe in patients with proximal hypospadias. In more proximal cases, the penile curvature is caused by an apoptosis of the urethral plate/corpus spongiosum due to the absence of androgenic stimulation resulting in a bend in the corpus cavernosa. The fibrous tissue, which is excised during correction of the curvature, is called chordee. The penile curvature in patients with more distal hypospadias is mostly caused by a deficient skin length or periurethral growth[1].

Classification of hypospadias

The classification of hypospadias is based on the severity of the malformation, and is of great importance, since the choice of surgical technique is based upon it. The term *severe* is, however, a subjective word, meaning different things to different surgeons and especially different patients and parents. This is why an objective classification system would be of great interest for both clinical use and research to be able to compare outcomes. The most common way of classifying hypospadias during external examination is by the position of the urethral opening, which may be distal (60-65% of cases), mid-penile (20-30% of cases) or proximal (10-15% of cases)[26] (**Figure 8**).

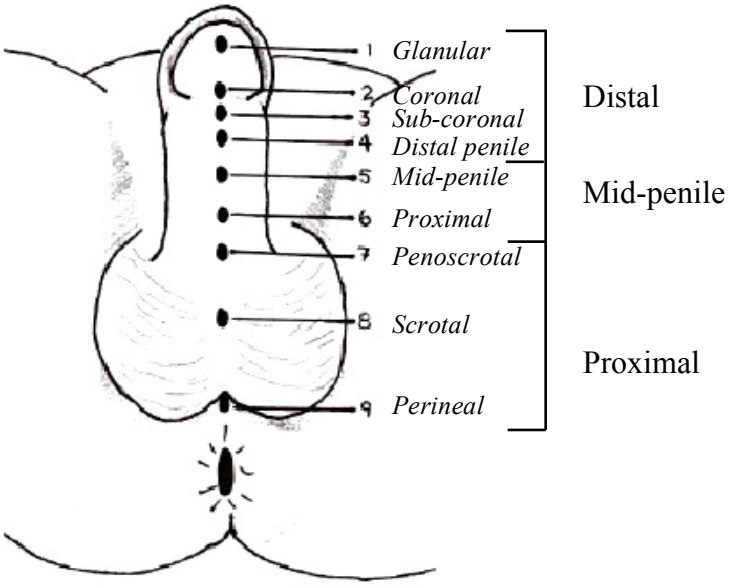

Figure 8. Classification of hypospadias according to the position of the urethral opening. Author's drawing.

However, this classification system does not take into account the quality of the urethra and the urethral plate, the degree of penile curvature or the division of the corpus spongiosum. A complete assessment which includes all these factors can only be carried out during surgery[27]. However, a primary assessment is important, to be able to inform the parents or patient about the treatment, if one or two surgeries are planned and the probable outcome. In a retrospective research setting, only the collected data is available for information, which is why classification is often based on a summary of data such as the position of the urethral opening, presence of penile curvature or surgical method.

Clinical symptoms

Boys born with hypospadias are at a risk of having meatal stenosis and this must be evaluated early because it can cause difficulties voiding. Otherwise, smaller boys have no symptoms. Later on during childhood they have varying symptoms depending on the phenotype. A mild hypospadias may cause only cosmetic dissatisfaction, while a patient with a more proximal hypospadias will not be able to urinate standing, and severe penile curvature could inhibit sexual intercourse. Urinary symptoms and long-term outcome is discussed further on.

1.6 MANAGEMENT

General aspects of hypospadias management

Timing of hypospadias repair is a much-debated question. Factors influencing timing are anaesthetic risk, penile size and psychosocial development. After six months of age, the anaesthetic risk is equivalent to the risk later during childhood, indicating that hypospadias surgery should not be performed before this age. The penile growth is very small between the first three months of life and the pre-school years, which is why this is not a reason for waiting. Genital awareness begins around 18 months of age, and after this the child is also more mobile and less cooperative[28]. However, one study did not show any differences between boys having had surgery before or after 18 months of age concerning psychosocial consequences such as psychological stress[29]. Most children have no memory prior to three years of age, and thus will not consciously remember their hospital stay if surgery is performed before this age[30].

A few decades ago, undergoing hypospadias surgery meant at least a week of hospital stay, often immobilized because of bandages and urinary diversions and separation from the parents. The trend today is towards single-stage repair during the first year of life undertaken as day-surgery and home-based care[28].

In Sweden, surgery is recommended between 9-18 months of age. The Section of Urology of the American Academy of Pediatrics recommends surgery between 6-12 months or during the 4th year[28]. Long-term follow-up studies of boys having undergone surgery at this young age will be able to increase our knowledge on whether this is the optimal age.

Surgical methods

The aim of hypospadias surgery is to create a urethra with a good function and to correct an eventual penile curvature resulting in a cosmetically normal penile appearance with a slit-like meatus on the tip of the penis[31]. There are a large number of surgical techniques described, and current trends and research influence which methods are most used for the moment.

The choice of surgical technique, however, mainly depends on the severity of the hypospadias and each institution chooses which techniques to apply in different circumstances. Not all cases need to be managed surgically for medical reasons. Glanular hypospadias with a fused glans proximal of the urethral opening and a ventral curvature <30% do not need a urethroplasty if the distance from the ventral lip of the meatus to the corona exceeds 2 mm according to some hypospadias surgeons[5]. The only reason for surgery in these cases is cosmesis, and a foreskin reconstruction or a circumcision can be performed depending on local culture traditions or parental preference[28]. In our institution, glanular/coronal hypospadias is repaired with a meatal advancement and glanuloplasty procedure (*MAGPI*).

The *MAGPI* procedure is applicable in patients with distal hypospadias without penile curvature, and consists briefly of an excision of the bridge of tissue between the meatus and the urethral groove, a transverse closure of the opening, and a reconfiguration of the glans. The procedure is combined with a foreskin reconstruction or a circumcision (**Figure 9**)[32]. No urinary diversion is needed post-operatively and the procedure is usually a day-case procedure.

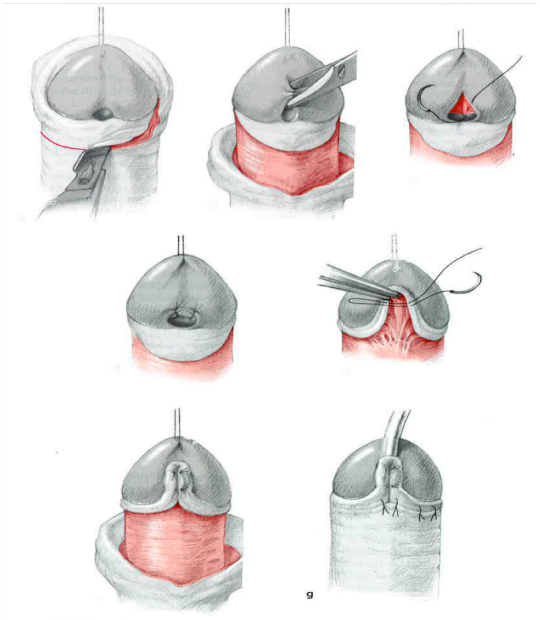

Figure 9. Meatal advancement and glanuloplasty (MAGPI) procedure. Picture from Hypospadias Surgery by Prof. Hadidi. Published with the kind permission of Springer.

Snodgrass or *Tubularized Incised Plate Urethroplasty (TIP) according to Snodgrass* is a method chosen for all degrees of penile hypospadias, and also in case of penile curvature if the urethral plate is sufficient after chordee correction[1,5,32]. The urethral plate is conserved and incised in the middle to make it wider, allowing the plate to be tubularized around a

stent. This results in a slit-like meatus located on the glans. A dartos pedicle flap covers the neo-urethra, and a glanuloplasty is performed (**Figure 10**). This procedure may also be combined with a foreskin reconstruction. A dressing and a urethral stent are kept for a week; the patients stay overnight, but can go home the next day with home health care[32].

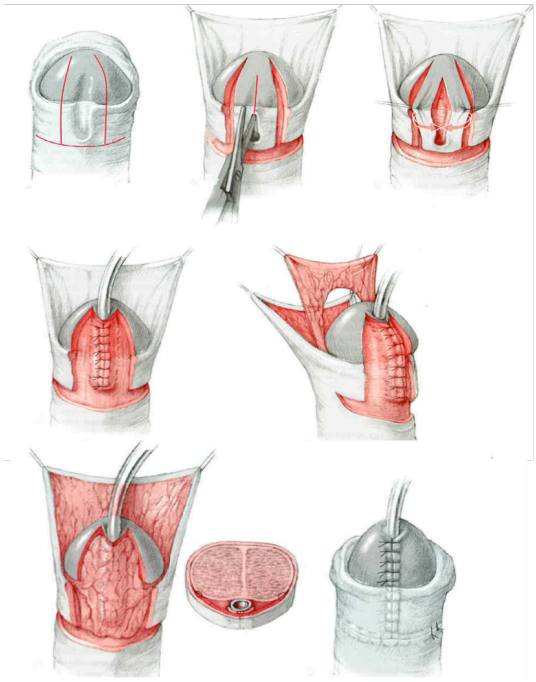

Figure 10. Snodgrass procedure or Tubularized Incised plate Urethroplasty for distal hypospadias repair. Picture from Hypospadias Surgery by Prof. Hadidi. Published with kind permission of Springer.

In patients with proximal hypospadias, with a penoscrotal, scrotal or perineal position of the meatus, combined with penile curvature and a bifid scrotum, either a *Duckett* procedure (*Tubularized Preputial Island Flap* repair) or a *Bracka* repair is performed.
The *Duckett* procedure consists of a transverse preputial island flap, which is tubularized and placed as the neoutrethra. The glans is incised in the middle to localize the neomeatus centrally[1]. These patients stay two days in hospital followed by home health care and keep the urinary diversion for two weeks (**Figure 11**).

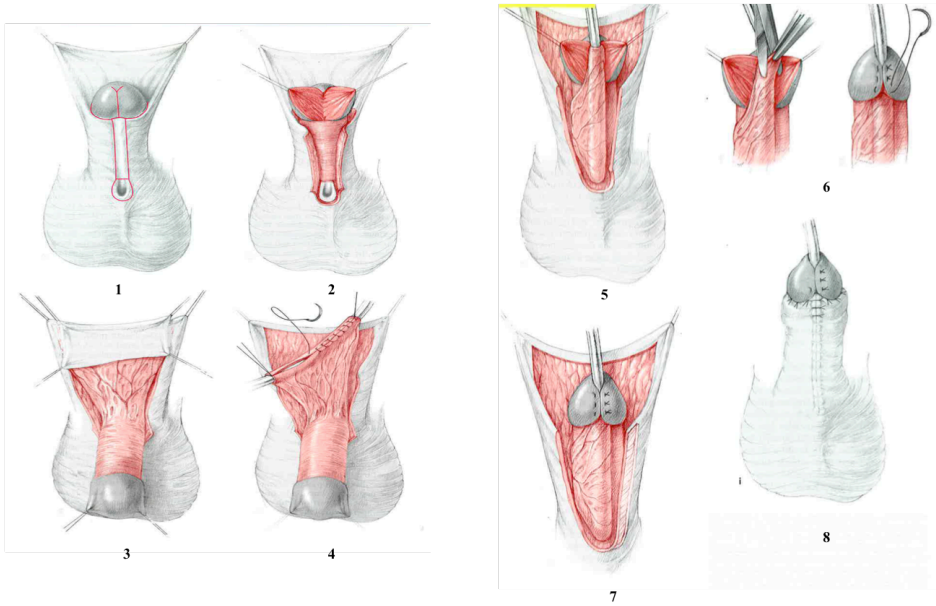

Figure 11. The Duckett procedure.
Picture from Hypospadias Surgery by Prof. Hadidi.
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The two-stage procedure according to *Bracka* is chosen in primary cases especially when the urethral plate is inadequate. It can also be used in redo cases with a preserved foreskin. The surgery is performed in two stages; a first step when the new urethral plate is created (**Figure 12**), and a second step when the urethral plate is tubularized[33] (**Figure 13**).

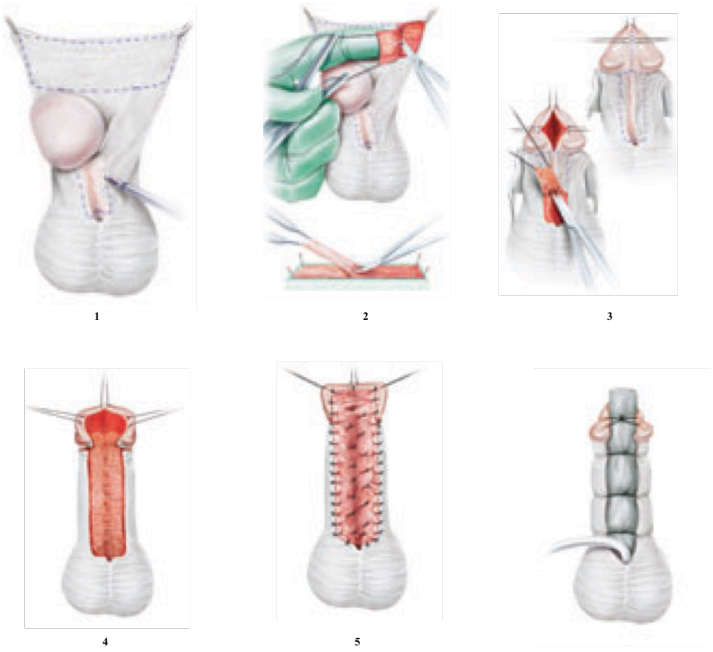


Figure 12. Two-stage Bracka repair; Stage I: The construction of a new adequate urethral plate. Surgery Illustrated - Surgical Atlas: Two-stage hypospadias repair with inner preputial layer Wolfe graft (Aivar Bracka repair) by Altarac, S. Published with kind permission of BJUI.

The existing inadequate urethral plate is excised, the glans clefted, and chordee excised. In case of primary surgery, a thin inner layer of the prepuce usually constructs the new urethral plate. Buccal mucosa or another graft could be used in case of previous circumcision, redo surgery or lichen sclerosus (LS). The graft is sewn into place and left to heal for 5-6 months. The second stage consists of a tubularization of the neo-urethral plate[33] (**Figure 13**).

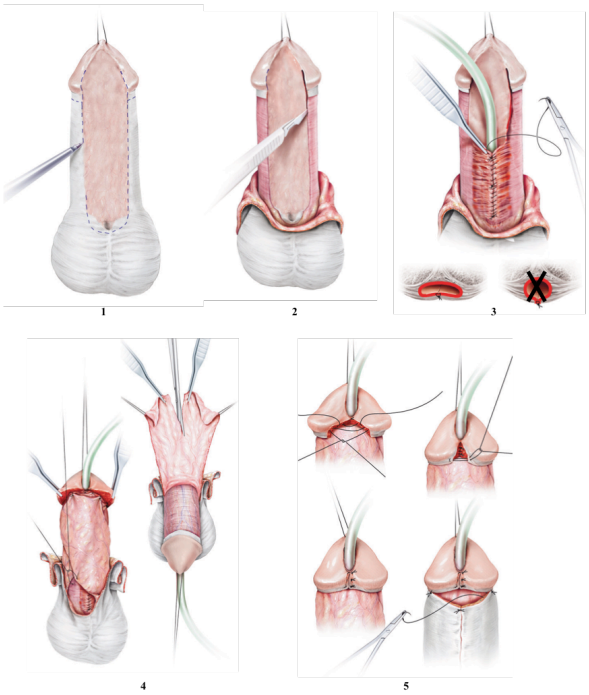


Figure 13. Two-stage Bracka repair; Stage II: The tubularization of the new urethral plate and glanuloplasty. Surgery Illustrated - Surgical Atlas: Two-stage hypospadias repair with inner preputial layer Wolfe graft (Aivar Bracka repair) by Altarac, S. Published with kind permission of BJUI.

In our study cohort, except for the above described and currently used techniques, the *Mathieu, Horton-Devine* and *Denis Browne* procedures were commonly used[1]. They are no longer used in our institution, but are still performed in other centres. The *Mathieu* procedure is applicable in cases of distal hypospadias and is a flap-based technique consisting of the creation of a meatal-based flap on the ventral side of the penis. The flap is flipped up and creates the ventral wall of the neo-urethra. *Horton-Devine* can be used in all types of proximal cases, and consists of a free full-thickness inner preputial graft used to create a neo-urethra. *Denis Browne* is a two-stage technique where the straightening of the penis is performed and the foreskin is divided and placed to cover the penile shaft. The second stage is performed later and consists of the creation of the neo-urethra from the ventral skin, either tubularized or just left to form a kind of fistula including the penile skin strip[1].

Surgical considerations

Risk factors for complications of hypospadias have been identified to be a proximal meatus, reoperation, and a glans width <14mm[5]. None of these factors are possible to influence preoperatively, except the glans width using preoperative testosterone. Studies on an eventual complication risk reduction after preoperative testosterone treatment show varying results however[34]. Proximal hypospadias surgery and re-do surgery present the greatest challenges. It is recommended that these should be concentrated on a single surgeon/surgical team in a centre to increase their experience and optimize the possibilities of a satisfactory outcome[5].

Post-operative follow-up

All four paediatric urology departments and two plastic surgery departments that perform all the hypospadias surgery in Sweden have put together a national surveillance plan with a case report form (CRF) based on current knowledge and research to optimize the care of all patients with hypospadias and also ensure that follow-up of good scientific quality is possible **(Figure 14)**.

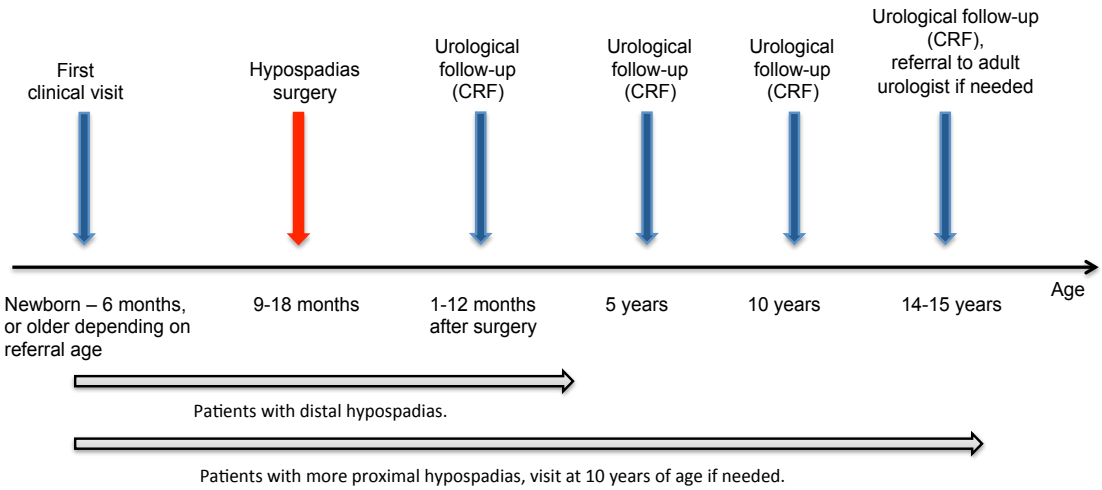


Figure 14. The Swedish national surveillance program for hypospadias. Adapted from Swedish Healthcare program for hypospadias.

The CRF contains all the data on the initial examination, surgery performed and surgical result after 1-12 months, 5 years, 10 years and 14-15 years of age. The same anatomical chart is reported at each visit with meatal location, meatal shape, urinary stream, direction of erection and eventual fistula. Uroflowmetry is also performed and the Hypospadias Objective Scoring Evaluation (HOSE) questionnaire is completed. At the last visit, genital measures are collected, and the patient is asked about erection, presence of ejaculation and sexual activity. The frequency of the visits depends on the phenotype, performed surgery and need of follow-up. Generally, after MAGPI surgery, the boys are only seen once after 1-12 months. After TIP, and surgery for more proximal hypospadias, they are also examined at 5 and 15 years of age and eventually at 10 years of age. All boys in need of continued follow-up and care are transferred to an adult urologist or andrologist after this point[32].

1.7 OUTCOMES AND OUTCOME ASSESSMENTS

"No matter what measures are taken, doctors will sometimes falter, and it isn't reasonable to ask that we achieve perfection. What is reasonable is to ask that we never cease to aim for it." - Atul Gawande, Complications: A Surgeon's Notes on an Imperfect Science.

Surgical results

Early complications, such as infections, are rare problems in hypospadias repair. Prophylactic antibiotics (one dose peroperatively) are given to all patients with a catheter left to drain the urine postoperatively, thus not after day-case surgery patients. Catheter blockage, meatal stenosis, ischaemic skin flaps, oedema, postoperative painful erections and bladder spasms may however appear, and the medical staff needs to pay attention to the early signs of these complications.

Urethrocutaneous fistula is the most common complication after hypospadias repair. The incidence varies between 0.5-20% and depends on the surgical technique, but has decreased during the past two decades. Once a fistula has formed, it is generally recommended to wait 6-12 months before attempting any repair. Most commonly, the fistula tract is excised, sutured and covered by several layers of tissue[1,35]. The second most common complications after hypospadias surgery are *meatal stenosis and urethral strictures*. Since modern surgical techniques seldom include circumferential anastomoses, the incidence of urethral strictures has decreased and surgical advances have also reduced the incidence of meatal stenosis. These complications may also be caused by LS. Both meatal stenosis and urethral strictures present symptomatically with voiding difficulties, urinary tract infections and urinary incontinence. Severe stricturing may lead to fistula formation, which is why a stenosis should be excluded before fistula repair. Clinical examination and uroflowmetry combined with a bladder scan generally provide the diagnosis. Dilatation and visual urethrotomy are the primary treatment options, but may be insufficient and require a more surgical intervention[1,35]. *Urethral diverticula and acquired megalourethra*, less common complications after hypospadias repair, may be caused by a distal urethral or meatal

stenosis or, in case of absence of a distal obstruction, a hypospadias repair creating an excessively wide neourethra. The lack of an adequate corpus spongiosum proximal to the reconstructed urethra allows the urethra to bulge out and may also create diverticula. Pathogenic factors such as a distal obstruction need to be eliminated to avoid recurrence before surgical repair, which consists of the excision of the redundant urethral tissue[1,35]. Beyond these most common complications, several other factors can require redo-surgery such as glans dehiscence, breakdown, persisting or recurrent penile curvature and cosmetic unfavourable outcome[36].

Complication rates depend on many factors, and their assessment is complex. Limited numbers of patients in studies, few studies comparing different techniques and a lack of standardized algorithms for the assessment of outcome make comparisons difficult. A surgeon's or clinic's technical learning curve and experience may also influence the incidence of complications, showing low complication rates, but not related to the choice of surgical technique. Most studies report complication rates after a short follow-up time, and even if the majority of complications appear during the first year post-operatively, adult urologists handle several cases of late complications-/ dehiscence, which is why long-term follow-up and the transition to adult care are important[36,37].

Lower urinary tract symptoms (LUTS)

Patients with hypospadias may present with an abnormal voiding pattern pre- as well as postoperatively. Urinary problems may be caused by the hypospadias itself or by surgery, such as a stiff urethra, a narrow urethral opening, terminal dribbling or fistulas. In patients with more proximal hypospadias, the urethral adaptability may be reduced because of a lack of corpus spongiosum. Long-term follow-ups on urinary problems are scarce and with diverging results, but terminal dribbling and hesitancy as well as spraying have been described[38,39].

Lower urinary tract symptoms (LUTS) refer to a group of symptoms including storage and irritative symptoms and voiding and obstructive symptoms[40]. They are generally described in patients with prostate problems, but can have different causes in both men and women. LUTS in men is most commonly evaluated using the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF), but these questionnaires concern especially prostate-related problems[41,42]. No disease-specific questionnaire exists to evaluate LUTS in men with hypospadias. The development of a disease-specific instrument to evaluate LUTS in patients with hypospadias would be of great interest.

Cosmetic result

The major cosmetic goals of surgery after hypospadias repair still need to be determined to fulfil patient satisfaction. With continuous development of surgical techniques, the results have improved significantly, but patient and parent dissatisfaction is still a problem[43-46]. Dissatisfaction with the penile appearance, in some studies mainly due to penile length and curvature, have been repeatedly reported, even if the majority of the studies are small and

lack validated instruments[44-48]. Follow-up and evaluation of the cosmetic result is therefore crucial. Several attempts have been made to assess the patient, parent and surgeon appraisal of the results after hypospadias surgery[49-52].

Objective scoring of the surgical result can be assessed by the *Hypospadias Objective Scoring Evaluation (HOSE)* or the *Hypospadias Objective Penile Evaluation (HOPE)*-score[53].

HOSE evaluates the meatal location, meatal shape, shape of the urinary stream, direction of the erection and eventual presence of fistulas with each domain scored between 1-2 or 1-4 depending on the item, with a lowest possible total score of 5 and a maximum score of 16. A score ≥14 is proposed to be considered as an acceptable result in the present era of hypospadias repair if the metal position is at least proximal glandular, there is a single urinary stream, and the angle at erection is moderate or less. It is a validated instrument with minimal interobserver variation[54]. *HOPE* is a validated instrument with good reliability and internal validity that includes all surgically correctable items including the position of meatus, shape of meatus, shape of glans, shape of penile skin and penile axis. The assessment of degree of abnormality is done by a urologist comparing the surgical outcome with reference pictures and standards for a "normal" penile appearance with the aim of being an objective outcome measure[53].

The patient satisfaction of the surgical result is at least as important, since the objective surgical result has very different consequences for different patients with different coping strategies. Weber et al. developed and validated an instrument to assess satisfaction with the cosmetic result after hypospadias repair, initially for children (The paediatric PPS), which was later validated for adult patients (Penile Perception Score, PPS)[55,56]. The score consists of four items referring to the look of the penis; meatal position and shape, glans shape, shaft skin shape and general penile appearance. Satisfaction with penile straightness may also be included. Satisfaction with penile length was included from the beginning, but not in the final version. A total PPS score can be calculated and used both to compare the satisfaction at different times in one individual and between groups. The score can also be used by urologists to assess the surgical result and compare patient satisfaction with surgeon satisfaction, both face-to-face with the patient and by objective scoring of photographs by an independent scorer.

"*Here is my secret. It is very simple: It is only with the heart that one can see rightly; what is essential is invisible to the eye."* From "The Little Prince" by Antoine de Saint-Exupéry.

Body esteem

Body esteem refers to self-evaluation of one's body or appearance. A negative perception of the genital organs may influence a person's body esteem. One study by Vandendriessche evaluated this matter in patients with hypospadias with reassuring results, but with few and young patients[57].

Several instruments exist to evaluate body esteem. Many are focused on the relation between body weight and body esteem. *The Body Esteem Scale for Adults and Adolescents (BES)*, has been developed from the original Body Esteem Scale for Children[58]. It is based on the concept that body esteem consists of three factors; a) general feelings about appearance, b) weight satisfaction and c) attributions of positive evaluations about one's body and appearance to others. It is a 23-item instrument with the degree of agreement scored on a 5-point Likert-scale ranging from 0 (*never*) to 4 (*always*), and negative items are reversely scored. In the evaluation and validation of the instrument, it was found that self-esteem is uniquely related to positive feelings about appearance, which implies that to a good way to improve self-esteem is to find methods to improve a person's feeling about his appearance.

Sexual function

A satisfactory sexual life is a part of the definition of Health according to the World Health Organization (WHO)[59]. A good hypospadias repair should enable a satisfactory sexual function, which is an important part of a good quality of life. A persisting penile curvature, scarring or an individual's negative perception of his genitals may have important negative consequences, both for sexual function, satisfaction and how a person dares to initiate intimate relationships.

Earlier follow-up studies on sexual function in men with hypospadias showed a delayed sexual functioning[60]. More recent studies have found a more positive outcome, with a good sexual functioning, and a good satisfaction with their sexual life. However, a lower satisfaction with the cosmetic result is often found to influence this result negatively and problems with erection and ejaculation have also been reported[44,48,61-65].

Validated measures for assessing sexual function have only recently been developed. The recognition of a relatively high prevalence of sexual dysfunction and disorder in our society and a large interest from the industry to produce treatments for these problems, have helped the development. Sexual dysfunction is often evaluated according to the sexual response cycle, consisting of sequenced and coordinated phases of desire, arousal, orgasm and resolution. Dysfunction can occur in one or several phases and is evaluated independently of aetiology. Most instruments end up in a score for each domain and a total score, and the majority are constructed to assess either female or male sexual functioning while a few assess both[66]. Very few studies have been published regarding these norms. One of the most widely used is the Derogatis Interview for Sexual Functioning (DISF-SR) consisting of 25 items and constructed for both men and women[66].

Fertility

There are few studies on fertility in men with hypospadias, but the fertility could potentially be lower in these men for several reasons[1,67].

Cryptorchidism, especially bilateral, is associated with a lower sperm density and is not uncommon in association with hypospadias[8,65]. A Swedish study found uni- or bilateral cryptorchidism in 6% of their patients with hypospadias[8]. In patients without hypospadias but with previously treated bilateral cryptorchidism, 79% had a sperm density less than 20 million/mL, while in a previously corrected unilateral cryptorchidism 31% had sperm density less than 20 million/mL)[68].

Testicular dysgenesis syndrome (TDS) is a combination of the symptoms of poor semen quality, testes cancer, cryptorchidism and hypospadias and is speculated to have a common underlying entity[69]. The imbalance between oestrogens and androgens during foetal life leads to an increased oestrogen exposure in utero, either caused by genetic defects or environmental factors such as oestrogen disrupters. This is believed to cause an impaired development of foetal testis and induce a disturbed Sertoli cell function and a decreased Leydig cell function resulting in TDS[68]. The role of oestrogen disrupters and their possible environmental oestrogenic or antiandrogenic effect on reproductive abnormalities in human males is however unclear, and is mainly shown in animal studies. Additionally, the hypospadias part of TDS is questioned. Only a very small fraction of men with hypospadias present with TDS.

Anatomical factors, due to the hypospadias itself, or the postoperative result, may also pose a problem to fertility. A persisting penile curvature can make intercourse with penetration impossible as well as a micropenis. Even though orgasm is normal in most men,

anejaculation is more frequently reported in this group[1,44,70]. Patients with a proximal hypospadias may lack the bulbospongiosus muscle, which is needed for the expulsion of the semen, causing anejaculation. A poor surgical result could also result in a baggy urethra or a diverticulum after a distal urethroplasty, which could slow down the ejaculation. In case of ejaculation problems, semen analysis, urethrography and a transrectal ultrasound evaluation should be employed to assess aetiology and treatment possibilities.

The patients with DSD including hypospadias have a higher incidence of azoospermia, oligospermia and abnormalities of the hypothalamic-gonadal axis, possibly resulting in infertility issues[71].

Asklund et al. investigated the reproductive function as well as fertility in men with isolated hypospadias (IH) and men with hypospadias associated with other genital disorders (HAGD), predominately cryptorchidism. They compared these with a control group, showing similar results of semen quality in the IH group compared with controls, but lower levels in the HAGD group (sperm density less than 20 million/mL in 42% as compared with 18% in the IH group)[65]. Men with HAGD also had more disturbed levels of follicle stimulating hormone and luteinizing hormone while men with IH only had slightly increased levels. Men with hypospadias in their registers were fathers to at least one child to a lower extent compared with controls.

The assessment of fertility is best made by semen analysis completed by an anatomical exam and hormone analysis. When this is not applicable, registers, with data on fatherhood, or questionnaires, can give information on paternity rate and reported fertility. Where paternity rate gives us the number of men being a father to at least one child, reported fertility represents the number of men ever having been part of making a woman pregnant, even if the pregnancy may not have resulted in a child in the end.

Gender-related development

Human psychosexual development consists of three different components; gender identity, the sense of being male or female, gender role behaviour, the assembly of characteristics that is seen as typically male or female, and sexual orientation, the sexual interest in persons of the same or opposite sex. Hormones as well as genetic and environmental factors influence this development. As hypospadias is often believed to be caused by a lack of androgens or androgen effect, there is an interest in the possible influence on the psychosexual development in these men and it has been hypothesized that men with hypospadias could have a more feminine gender role behaviour and identity[72-75]. Similar studies on the effect of androgens on behaviour have been conducted in girls and women with the genetic disorder Congenital Adrenal Hyperplasia (CAH). CAH is caused by an adrenal enzyme deficiency resulting in a lack of cortisol and aldosterone and, via feed-back mechanism, high levels of androgens instead. The girls are born with different degrees of masculinization of the external genitalia, and in some, this may result in uncertainty concerning sex assignment at birth. In this group of women, a more masculinized gender

role behaviour has been seen, both in childhood and adulthood concerning play behaviour, choice of profession and leisure activities and also a reduced heterosexual interest and a lower satisfaction with the assigned female sex[76,77].

Gender identity, gender role behaviour and sexual orientation can be assessed with the Gender/Sex questionnaire constructed by Hines[78]. This is a 12-item questionnaire with half of the items inquiring about the past 12 months and half about the person's lifetime. Responses are made on a Likert scale ranging from 1 to 7 with answers from *always* to *never*. Answers to the questions concerning sexuality range from *exclusively heterosexual* to *exclusively homosexual*. A sum score for gender identity, gender role behaviour and sexual orientation is calculated accordingly and a lower score indicates a more sex-typical gender role behaviour, more satisfaction with the sex of assignment and a more heterosexual orientation.

Psychosocial outcome

A psychosocial assessment should cover a person's social status, his functional capacities in society, and an evaluation of his mental health.

Being born with a congenital malformation treated surgically may present several risk factors for a negatively influenced psychosocial adaptation[60,79-81]. Hospitalization, repeated surgery and clinical examinations are potential stress factors for these children[82]. A study by Blotcky and Grossman showed that children having gone through genitourinary surgery had increased emotional disturbances compared with children having had ear nose and throat surgery[83]. This study was however performed on a small number of children having undergone surgery between 1970 and 1971, and another study showed no such adverse outcome[84]. The medical care of children today has changed dramatically during the last few decades. Boys operated for hypospadias stay mostly only over-night in the hospital together with their parents, and thereafter are cared for in their homes, followed by stent removal at home, by a medical team. The change of attitudes towards surgery at a younger age (before 18 months) has also had an impact, since the children will have no memory of this first hospital visit while growing up. In case of repeated surgery, and when the child is older, information to the patient and parents as well as psychological support if needed is of great importance. To avoid creating stigma, genital examinations should only be performed when necessary. A sense of control of the events around the child, of the information given and control of self, are of great importance to promote coping in the child[1].

A lower self-esteem, and a distorted image of their body could have an impact on the development of social competences. To dare to approach people and create relationships and to participate in activities requiring, for example, changing clothes in locker rooms could be a problem. Berg et al. showed in the early eighties that adult men with hypospadias showed shyness and were teased more as children, and behavioural difficulties were also shown by Sandberg et al., but these results were not found in a larger material in a later study by Mureau et al.[73,79,85].

Academic achievement may be interfered with, due to repeated hospital visits or in cases where bullying by peers, because of genital differences, make the school environment unfriendly. Berg et al. could show that the patients in their study had lower qualified professions than controls, but comparable levels of education and profession have been shown in several later studies[61,79,82,85].

Quality of life (QoL)

"Very often the same man says different things at different times: when he falls sick he thinks health is happiness, when he is poor, wealth"- Aristotle (384-322BC) in Nichomachean Ethics.[86]

It has been stated that there are as many definitions of quality of life as individuals, showing that individuals differ in what they find important[87] (**Figure 15**). The importance of what is important in life also differs in time depending on the situation for an individual[88].

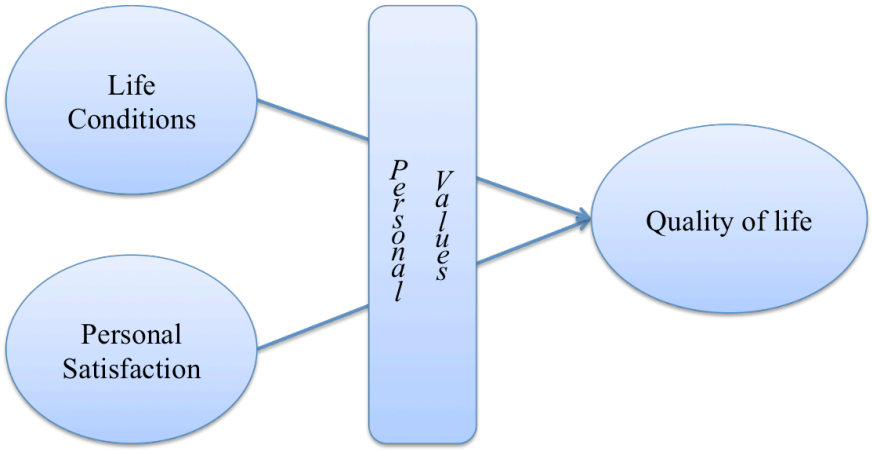


Figure 15. Quality of life defined as a combination of life conditions and satisfaction weighted by scale of importance.

The World Health Organization (WHO) defines health to be "an individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[89].

Quality of life is a subjective measure, and needs to, if possible, be assessed by the concerned person. Depending on the area of application, quality of life takes on different measures, and many different types of measurements have been developed[86]. There are two main approaches to measure quality of life in the health care area; to assess general health-related generic QoL (HRQoL) and symptom-specific QoL. Health-related generic QoL assesses how an individual's well-being may be affected over time by a disease, disability or disorder, and is independent of a specific disease. This allows comparisons between different groups of patients with different diseases for example. Since they are developed irrespectively of a disease or a condition of the patient they may often be applicable also to healthy people, allowing healthy comparison groups. Symptom-specific QoL

measurements are developed to specifically focus on issues relevant for the disease under assessment.

Quality of life in patients with hypospadias has been very sparsely investigated. A few studies on children and adolescents with hypospadias showed a comparable health-related quality of life in patients and controls, as well as one study in adults[90,91,92].

The Psychological General Well-Being Index (PGWBI) is one of the most widely used patient-reported HRQoL outcome measures. It produces a self-perceived evaluation of psychological general well-being and has been validated in many countries in large populations and on specific patient groups[93]. The instrument includes six dimensions: Anxiety, Depressed Mood, Positive Well-being, Self-Control, General Health and Vitality inventing emotional and affective states during the previous week. It has 22 items scored 0-5 with a higher score representing a better outcome.

Attachment processes

A person's ability to bond with or attach to other people may be influenced, both positively and negatively, by a disease or malformation, for example by hospital visits, surgery and cosmetic result and clinical exams, causing strain on the family[94].

Piglet sidled up to Pooh from behind. 'Pooh!' he whispered. 'Yes, Piglet?' 'Nothing,' said Piglet, taking Pooh's paw. 'I just wanted to be sure of you.' – A.A Milne
Illustration by E.H. Shephard, modified by the author.

John Bowlby, known as the father of attachment theory, described attachment as "lasting psychological connectedness between human beings" and attachment theory concerns "the propensity of human beings to make strong affectional bonds to particular others"[95]. He hypothesized that an attachment system evolved to protect infants in situations of danger or threat by maintaining the proximity between child and infant. Mary Ainsworth, the other founder of modern attachment theory, described attachment systems to be developed to give a child a sense of "felt security" to dare to explore it's surroundings[96]. The degree to

which a child has come to rely on the attachment figure and the response of separation qualifies the pattern of attachment. In experimental studies with infants, three different patterns of attachment were defined: secure, anxious-resistant, and avoidant. The secure attachment pattern includes children who welcome their carers return after a separation, and, if distressed, seek proximity and are easily comforted, while the children classified as anxious-resistant are more difficult to comfort when the carer comes back and show ambivalent behaviour. Finally, the children classified as avoidant, avoid interaction or proximity when the carer returns[96]. Bowlby's theory says that children's early relationship patterns with their caretakers form a prototype for relationship patterns later in life. In the working models of attachment, he also identified two key features, the child's image of the self and of others[97]. Attachment relationships continue to be important throughout life, and several approaches to attachment theory in adults have been made.

A four-category model, based on the model of the self and the model of the other by Bowlby, has been used to create the attachment style instrument, the *Relationship Questionnaire* (RQ), assessing attachment styles[97]. RQ is an adaptation by Bartholomew of the attachment measure developed by Hazan and Shaver (1987). The model is based on four combinations between the model of self and the model of others, hypothesizing that ones' model of self is either positive or negative (the self as worthy of love and support or not) as well as the model of others (other people are seen as trustworthy and available vs. unreliable and rejecting). The attachment patterns are derived from the combinations of the two dimensions (**Figure 16**).

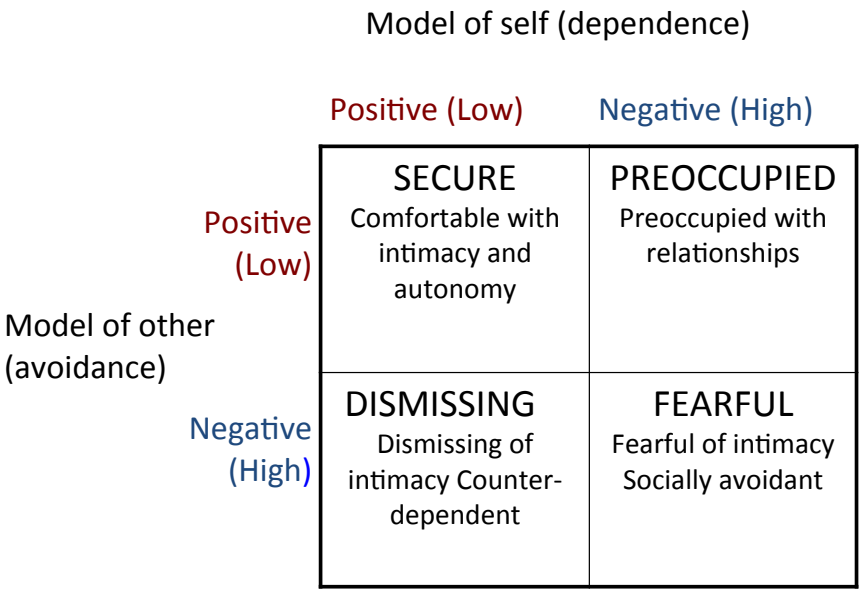


Figure 16. Model of attachment patterns according to Hazan and Shaver.

The SECURE cell indicates a sense of worthiness in combination with the trust that people will be accepting and responsive and corresponds to the label "securely attached". The PREOCCUPIED cell includes persons striving for self-acceptance by achieving the

acceptance of others, a combination of unworthiness and a positive evaluation of others. The people in the DISMISSING group avoid close relationships to protect themselves against disappointment since they have a negative disposition towards other people. In this way they succeed in maintaining a feeling of independence and invulnerability. Finally, the FEARFUL group contains people who avoid close relationships since they believe they would be rejected. They expect others to respond negatively to them and have a sense of unworthiness. The dependency on the horizontal axis signifies the level on which a person needs to be confirmed by other people to establish a positive self-regard, while the avoidance on the vertical axis shows the degree to which a person avoids relationships as a result of their expectations of rejection. By responding, on a seven-point Likert scale, to which degree a person resembles each of the four styles and also by choosing the style to which he resembles the most, the measure gives an evaluation of a persons' attachment style.

Psychiatric outcome

Psychological development and psychiatric outcome in men with hypospadias has been little investigated, but a few early studies showed an increased frequency of anxiety, signs of depression, and a less externalizing behaviour[80,82]. Recent epidemiological results have shown an increased prevalence of intellectual disability, autism spectrum disorders (ASD), ADHD and behavioural/emotional disorders in men with hypospadias compared with controls[98]. Possible factors causing adverse psychological effects in men with hypospadias have been proposed to be common genetic factors, the surgical procedures, or the hypospadias in itself.

There are many different measurements for psychiatric outcome depending on which aspect and which group of patients is to be examined.

ADHD Self-Report Scale

ADHD (Attention-deficit/ hyperactivity disorder) is one of the most common childhood developmental psychiatric disorders with a worldwide prevalence of 5-7% among school children, and it sometimes persists into adulthood[99,100]. Today, adults are also diagnosed with ADHD, and there are probably lots of undiagnosed cases with an impaired functioning because of their diagnosis[101].

The *ASRS-S-A* Screener is the validated screening version of the Adult Self-Report Scale (ASRS) © version 1.1., which screens for adult ADHD. It consists of six questions answered with a Likert scale and has an excellent specificity (99.5%) and an adequate sensitivity (68.7%). A score ≥ 4 indicates symptoms of ADHD. It may be used as a diagnostic tool, not to diagnose, but to indicate that pursued diagnostics should be carried out, and to screen a population. Used as a screening tool in a research setting, a score ≥ 4 is considered a positive outcome. A high score may however be related to anxiety, depression or mania, which has to be excluded before a clinical diagnosis is set[102].

Comprehensive Psychopathological Rating Scale- Self-Rating Scale for Affective Syndromes

Self-rating scales in psychiatry are generally considered to be of less value than clinician-based instruments both in clinical settings and research[103]. The CPRS-S-A has, however, been found to be a tool that is both useful clinically and for research purposes. It is a screening instrument for depression, anxiety and compulsive-obsessive disorders composed of 19 items. The responses are made on a 7-grade Likert scale, and a score for each subscale is calculated, with a higher score corresponding to more perceived anxiety, more perceived depression and obsessive-compulsive composure. The sub-scales have a cut-off score at ≥6 points confirming the suspicion of clinical depression/-anxiety or compulsive-obsessive disorder. Since CPRS-S-A is only a snapshot of the actual status of a person, a clinical evaluation has to be made to be able to set a diagnosis. In a research setting the instrument can be used to identify the prevalence of affective symptoms.

Mini-International Neuropsychiatric Interview

MINI is a short structured interview for DSM-IV and ICD-10 psychiatric disorders designed for both research and clinical settings[104]. Several widely used psychiatric structured interviews exist, but there was a need for a shorter version with accurate outcome, which is why MINI was developed in 1998 by David V. Sheehan et al[104]. The goal was to design an instrument that was short and inexpensive, easy to administer and with a high specificity and validity, which was achieved. It is compatible with ICD-10, the International Classification of Diseases as well as the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. In a clinical setting, it was designed to capture routine and repetitive information, leaving the specialist time for more important tasks during the time with the patient. Different professional interviewers other than a psychiatrist may administer the MINI, saving money and time. To avoid missing patients with true symptoms of disorders, the design was made a little over-inclusive, with a few more false positive answers, since the psychiatrist, when meeting the patient, will be able to rule these out. The disorder diagnoses included in the MINI are found in **Table 1**.

Table 1. Disorder diagnoses available in the MINI

Major depressive disorder	General anxiety disorder	Bulimia
Manic or hypomanic disorder	Agoraphobia	Addictive disorder
Melancholia	Social phobia	Alcohol dependence/abuse
Dysthymia	Post-traumatic stress disorder (OTSD)	Substance dependence/abuse
Suicidal risk	Obsessive compulsive disorder (OCD)	Psychotic disorder
Panic disorder	Anorexia nervosa	Antisocial personality disorder

1.8 INCENTIVES FOR THIS THESIS

More than 300 boys are born with hypospadias in Sweden each year, making hypospadias one of the most common congenital malformations and consequently many thousands around the world are affected. The result is that a large number of men live with this condition their whole lives.

Much is known about the genetic causes and pathogenesis as well as the surgical outcome after different surgical techniques, but the long-term results on especially psychosocial and psychosexual function are more scarce and varied, particularly in men with proximal hypospadias.

Psychiatric morbidity in society is increasing, and hypospadias in itself, as well as surgical procedures, hospitalisation and the surgical outcome have all been hypothesized to cause an adverse effect on psychological functioning in men with hypospadias.

To be able to offer the best possible health care to this group of patients, an increased understanding of how living with hypospadias weaves into the complexity of an individual's life is crucial.

2 AIMS

The overall aim of this thesis was to increase the knowledge of the long-term aspects of hypospadias.

To achieve the overall aim, the specific objectives were:

Study I

- To assess the urological results in adult men born with hypospadias.
- To assess cosmetic satifsaction in adult men after hypospadias surgery.

Study II

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

Study III

- To inquire if men born with hypospadias have a satisfactory psychosexual outcome and normal fertility.

Study IV

- To study the prevalence of symptoms of psychiatric disorders in adult men born with hypospadias.

3 MATERIAL AND METHODS

3.1 AT A GLANCE

	Population	Material	Method
I	167 patients, 19-54 years old, included in the study from a cohort of 1030 patients born with hypospadias. 169 age-matched controls, 19-48 years, from the Swedish Population Register (SPR) and 47 controls circumcised because of phimosis.	*Questionnaire study:* Penile Perception Score (PPS), Body Esteem Scale (BES), and questions about the surgical outcome and LUTS. *Clinical study:* Anatomical evaluation, photo documentation and uroflowmetry.	Descriptive statistics in terms of population characteristics, surgical out-come, anatomical measurements and voiding function. Correlations between BES and PPS were analysed with Kendall's tau test. ANOVA and logistic regression was used for the PPS analysis, as well as satisfaction with penile length.
II	Same patients as in study I. Same controls as in study I, but the 47 circumcised controls excluded.	*Questionnaire study:* Psychological General Well-Being (PGWB), Relationship Questionnaire (RQ), questions about psychosocial situation as family situation, education, spare-time activities, bullying and medical status.	Descriptive statistics in terms of psychosocial situation, PGWB and RQ. Pairwise tests between groups when appropriate. Associations between two continuous variables were analysed with Spearman's rank correlation coefficient.
III	Idem as in study I.	*Questionnaire study:* Questions about fertility, sexual function, satisfaction and negative influence, PPS, PGWB, and a questionnaire by Hines about gender identity, sexual orientation and gender role behaviour.	Descriptive statistics in terms of fertility, sexual function, negative influence and gender issues. Pairwise tests between groups when appropriate. Associations between sexual satisfaction, PPS and penile length were assessed with logistic regression, and between PGWB and sexual satisfaction with quantile regression.
IV	Idem as in study II.	*Questionnaire study:* Adult ADHD Self-Report Scale (ASRS), and Comprehensive Psychopathological Rating Scale–Self-rating scale for Affective Syndromes (CPRS-S-A). *Clinical study:* Mini International Neuropsychiatric Interview (MINI).	Descriptive statistics in terms of prevalence and comparison of means.

3.2 METHODOLOGICAL ASSUMPTIONS

A paradigm is a belief system that guides our way of doing things and the research we conduct will always be influenced by the researcher's way of doing, seeing and interpreting things. In philosophy of knowledge, Guba described a paradigm as a basic set of beliefs that guides actions or how we view knowledge, how we see ourselves in relation to this knowledge and the methodological strategies we use to discover it[105]. Different settings traditionally use different paradigms, and the medical research paradigm stems from the positivistic tradition, based on an objective truth that the researcher observes and reports. The methodology is then experimental and based on hypotheses, which are rejected or confirmed. Today, most medical research is conducted in a post-positivistic paradigm manner, pursuing objectivity, but with the acceptance that theories, background, knowledge and values of the researcher can influence what is observed, thus recognising the possible effects of biases. The research conducted for this thesis is positioned within the post-positivistic tradition.

3.3 PARTICIPANTS

Patients with hypospadias

The origin of this patient cohort consists of 571 patients with hypospadias collected by a paediatric urologist, Dr Brodsky, at the St. Görans Children's Hospital in Stockholm between 1970 and 1984. This material was completed with patients above 18 years of age, at the time of inclusion, who once received the diagnoses of hypospadias in the Stockholm and Gothenburg areas between 1984 and 1994. All patients (n=1030) were contacted and invited to participate. Patients with the wrong diagnosis or an inability to speak or understand Swedish were excluded. Those that responded, received a set of questionnaires (n=197). The response rate of the total cohort was 16%. Eighty-five per cent of the participating men with hypospadias completed the questionnaire (**Figure 16**).

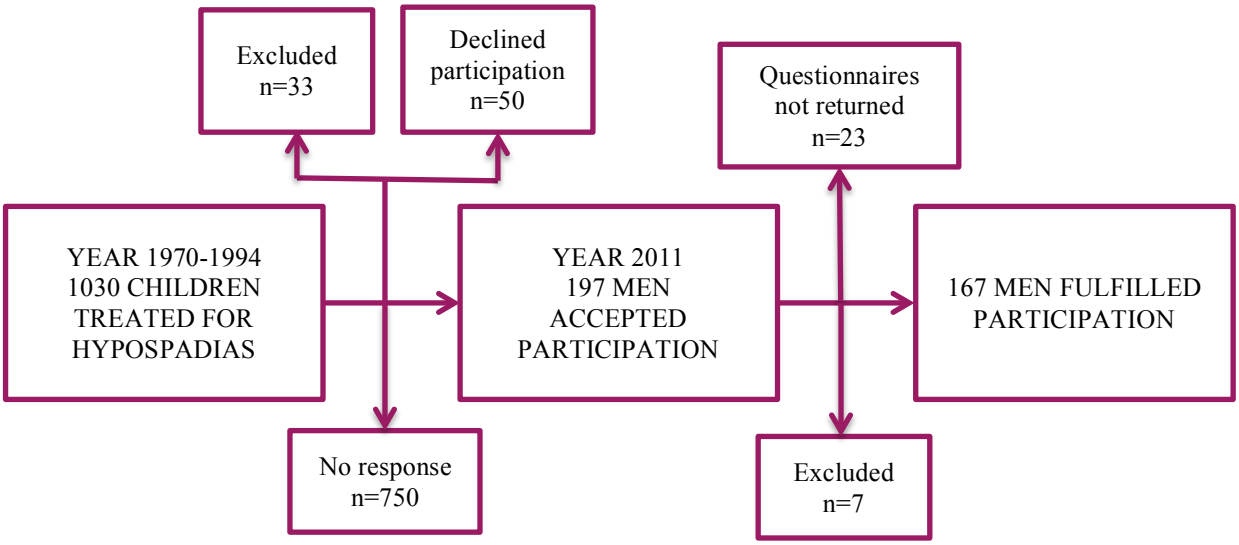


Figure 16. Flow-chart of the patient cohort.

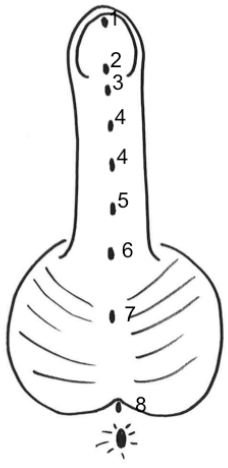
A drop-out analysis showed that the mean age of the original cohort and the participating study patients was comparable. Among the patients with known phenotype, the phenotype distribution was comparable, with the majority of patients having a distal type of hypospadias, followed by mid-penile hypospadias and about 10% with a more proximal type (**Table 6**).

Table 6. Comparison of eligible population and study patients

	Eligible population	**Study patients**	***p*-value**
Age years Mean, (SD)	34.8 (7.7)	34.3 (8.4)	0.54*
Phenotype n (%)			
Distal	261 (54.1)	105 (62.7)	0.05**
Mid-penile	166 (34.4)	40 (24.1)	
Proximal	55 (11.4)	22 (13.3)	
Unknown	351	0	

*Students t-test **Pearson's Chi-square

The mean age of the patients was 34 years of age (19-54 years) at the time of the study and the mean follow-up time since surgery was 29 years (6-48 years). Patient charts were studied regarding the degree of hypospadias, which was classified as distal, mid or proximal, according to the meatal positioning pre-operatively, as well as number of surgical operations, surgical method and complications found in the patient chart. The mean number of surgical procedures increased with increased severity (**Table 7**). Thirteen patients, 10 with glanular and 3 with distal penile hypospadias, had not had surgery.



Meatal positioning	**n**	**Severity**	**n (%)**	**Surgical procedures (n) Mean (SD)**
1. Glanular	53	Distal	105 (63)	1.57(1.1)
2-3. Corona glandis and distal penile	52			
4-5. Penile	40	Mid-penile	40 (24)	2(1.47)
6. Penoscrotal	14	Proximal	22 (13)	3.4(3.0)
7. Scrotal	6			
8. Perineal	2			

Table 7. Characteristics of the study patients.

Patients with proximal hypospadias and every other patient with milder hypospadias were invited to the hospital for an outpatient visit of which 47 patients accepted. If they declined the outpatient visit they were invited to only answer the questionnaire.

Controls

The main control group was recruited from the Swedish Population Register (SPR). Eight age-matched men per recruited patient were contacted (n=1362) with a response rate of 14%. The responders (n=186) received the same questionnaire as the patients (questions specifically concerning hypospadias excluded). Ninety-one per cent of the participating controls completed the questionnaire. The control group had a mean age of 33 years of age (19-48 years). Controls from the SPR were also recruited to the outpatient visit, but since the interest was low (n=11), this recruitment was completed by advertisement at the medical universities of Karolinska Institutet and the Sahlgrenska Academy (n=38). In total 49 controls attended the outpatient visit.

Controls having had surgery for phimosis

With the aim of being able to compare another group of men also having had genital surgery at a young age, and with a comparable cosmetic result as the majority of the hypospadias patients, a group of men having undergone surgery because of phimosis with circumcision as children was included. These patients were found from our local patient register and contacted by post. Those that responded (n=47) received the same questionnaire as the patients (questions specifically concerning hypospadias excluded). The circumcised control group had a mean age of 26 years of age (19-44 years) at the time of the study.

3.4 METHODS

Study outlines

All four studies were conducted as cross-sectional long-term clinical follow-up studies.

Patients and controls received a questionnaire, either by post or by e-mail. The administered self-completion questionnaire was constructed of several validated instruments completed by questions constructed by the research group. It aimed to evaluate the urological, psychosocial, psychosexual and psychiatric outcome of men being born with hypospadias. In total, it consisted of around 300 questions divided into several parts, with most questions being structured questions, in some cases completed with unstructured voluntary questions for free comments. The questions constructed by the research group included in the questionnaire are included as **Appendix A**.

Studies I and IV also included a clinical visit for a sub-group of patients and controls (**Figure 17**). During this visit a urologist performed a clinical exam and a uroflowmetry was carried out. The outpatient clinic patients and controls also underwent a psychiatric screening.

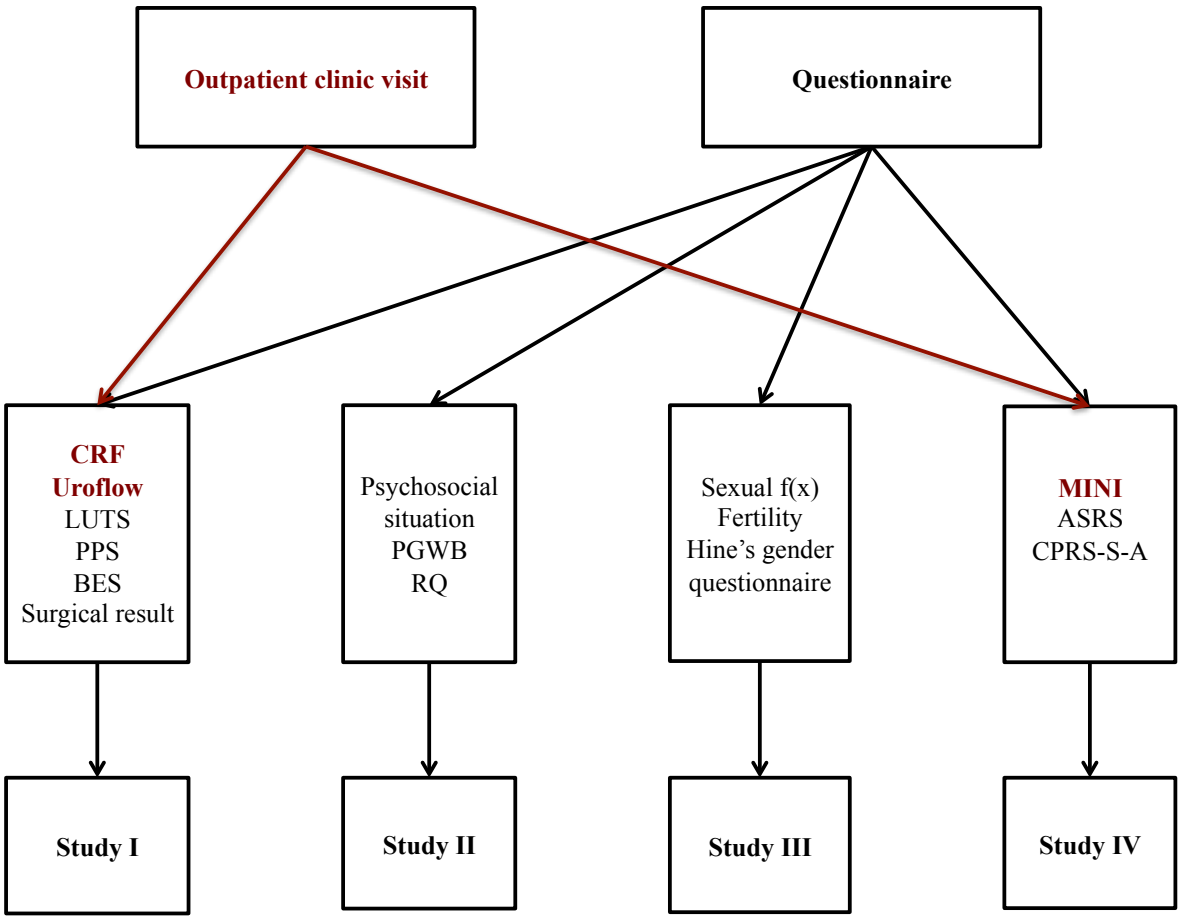


Figure 17. Flowchart of the study.

Questionnaire studies

Questionnaires are a method used to collect standardized data from a large number of people, i.e. the same data is collected in the same way, which makes statistical analysis possible. We have used two different types of surveys; factual surveys collecting descriptive information, such as level of education, and attitude surveys, which collect people's attitudes and opinions[106]. The questions in a questionnaire may be structured or unstructured. Structured questions include dichotomous questions, with two possible responses, i.e. yes/no, questions based on levels of measurement, either with a nominal question, that is without ranking, i.e. different levels of education, or an ordinal question, where responders are asked to rate the answer options or a measure on an interval scale. One of the most common interval level question types are called Likert scales, with a bipolar ranking scale from, for example, 1-5 with 3 being the neutral point and the two ends of the scale are the opposite positions of the opinion. Likert scales are used in several of the validated instruments in this study, such as PPS, BES and the gender questionnaire by Hines. Unstructured questions, or open-ended questions, have an advantage of being able to capture a wider range and the flavour of people's answers, and the influence of the pre-determined possible responses in structured questions is avoided. To allow the participants to develop their answers beyond the structured questions, all sections were completed with open-ended questions. Needless to say, the construction of the questions is of great importance to be able to draw correct conclusions regardless of the type of questionnaire.

Method study per study

Study I

Outpatient clinic visit measurements

The outpatient visit was conducted following a Case Report Form (CRF) (**Appendix B**). The CRF contained all questions and genital measures to be taken by the urologist. The CRF was initially constructed by a national team of urologists to ensure that all the investigators performed the clinical exam in the same way as in the follow-up of DSD males. Instructions on how to perform the genital measurements were included. The CRF data were coded and transferred into a data file.

Urological outcome

Available measurements concerning LUTS are not adapted to investigate the urological outcome in hypospadias patients. Our research group therefore constructed questions based on known LUTS problems in patients with hypospadias. Patients and controls participating in the outpatient clinic visit also had a uroflowmetry, which was interpreted by our urotherapist.

Cosmetic result and body esteem

To evaluate the genital appraisal, PPS was used. Satisfaction with penile length was included in our study, even if it is no longer included in the final version of the PPS. Both scores on individual items and a total PPS score were calculated and used to compare the satisfaction between groups. To be able to compare the assessment of the surgical result with patient satisfaction, five independent scorers, physicians from different areas of expertise, scored photographs of the genitals, and the scores were compared. PPS was also used in *Studies II and III* in regression analysis concerning different aspects. Body esteem was analysed with the Body Esteem Scale. This was considered appropriate since it succeeds in differentiating feelings of appearance from feelings about weight, and weight was not an issue in this study. BES was also analysed in correlation with PPS.

Study II

The psychosocial situation of the participant was identified by questions concerning family situation, education, occupation, spare-time activities and country of birth. Childhood experiences, such as bullying and the negative influence of hypospadias on relationships with family and friends as well spare time activities, were also subject to inquiry. According to the study by Frisén et al., education and occupation was classified according to sex distribution based upon the Swedish Statistical Database[77]. “Male-dominant occupation” was defined as no more than 25% of females in the profession and “extreme-male dominant occupation” as no more than 11% of females in the profession.

Health-related quality of life was measured with PGWBI. There is no disease-specific quality of life instrument concerning hypospadias, which is why this could not be analysed. The ability to attach to other people was assessed by RQ.

Study III

Sexual function assessment

The questions in our study used to assess sexual function were based on a former study on women with DSD performed by the same research group[107]. The questions were adapted to concern males. Sexual satisfaction was assessed with a "yes/no-question", and analysed in association with phenotype, genital appraisal (PPS), penile length, presence of partner and health related quality of life (PGWBI).

Reported fertility

Fertility was assessed by questions concerning the presence of biological children or the history of making a woman pregnant. The reported fertility was then "to have ever made a woman pregnant". Questions about ejaculation problems, fertility issues, and wishes for children were also asked.

Gender-related development

Gender identity, gender core role and sexual orientation were assessed using a questionnaire by Hines [78].

Study IV

Patients and controls coming to the outpatient clinic underwent a short structured psychiatric screening interview (MINI) based on DSM-IV and ICD-10 psychiatric disorders. Trained professionals performed the interview, and the subjects were referred to further psychiatric counselling if needed. All participants filled in the ASRS, a screening measure for ADHD, and CPRS-S-A, an instrument constructed to detect depression, anxiety and compulsive-obsessive disorders.

3.5 STATISTICAL ANALYSIS

Overall statistics

Statistical methods and data analyses are presented in detail below. A summary of the statistical approaches can be found in **Table 3**. Statistical analyses were performed using <R Core Team (2016). R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria (*Studies I, II and III*) and SPSS Statistics ver. 22 (*Studies I, II, III*) and ver. 23 (*Study IV*). For *Studies I-IV*, a p-value ≤0.05 was considered statistically significant.

Statistical method	Study I	Study II	Study III	Study IV
Descriptive statistics	X	X	X	X
One-way ANOVA				X
Pairwise tests		X	X	
Kendall Tau	X			
Independent ANOVA	X			
Linear regression	X			
Logistic regression	X		X	
Spearman's rank correlation coefficient		X		

Table 3. Statistical approaches in the studies.

Descriptive statistics

Continuous outcome explained by continuous factors was analysed with Spearman's rank correlation coefficient, a non-parametric test, since there was no linear relationship between the factors and the outcome (*Study II*) and with Kendall's tau test, a non-parametric test appropriate for discrete variables (*Study I*). Continuous outcome with categorical factors with only two independent groups (i.e. patients and controls) was analysed with the parametric test Independent T-test (*Study I*), or its non-parametric version Mann-Whitney U-test (*Studies I, II, III and IV*) as appropriate. Kruskal Wallis is an extension of the Mann-Whitney U-test, and was used if more than two groups were being compared (*Studies I, II and III*). Categorical data were analysed with the Pearson Chi^2-test or Fishers' exact test, both parametric tests, depending on the number of expected counts (*Studies II, III and IV*).

Study I

The data from the two control groups (general age-matched controls and circumcised controls) were analysed separately. The results from the circumcised control group were analysed when the questions concerned the hypothesis regarding outcome after genital surgery and lack of foreskin. The satisfaction with the cosmetic result was adjusted both for several categorical variables, such as phenotype, with ANOVA, and for continuous covariates, such as penile length, by regression

analysis. Logistic regression was also used to calculate the "odds of being satisfied" with the cosmetic result by adjusting for phenotype and age at surgery as well as satisfaction with penile length, also adjusted for phenotype and penile length.

Study II

Pairwise tests between groups were used when appropriate.

Study III

When analysing the questions concerning glanular sensitivity, all circumcised controls, from both age-matched controls and the circumcised group, were analysed together and compared with all the operated patients with hypospadias. Analysis between satisfaction with sexual life and satisfaction with the cosmetic result, penile length, presence of partner, and phenotype, respectively, were performed with logistic regression analysis. Analysis between HRQoL (PGWBI) and satisfaction with sexual life was analysed with quantile regression estimating the conditional median of the PGWBI score in relation to satisfaction with sexual life. Pairwise tests between groups were used when appropriate.

3.6 ETHICAL CONSIDERATIONS

Research on hypospadias involves important ethical issues. Representatives from the Swedish patient organization for patients with DSD, as well as DSD patient organizations in other countries, have requested more follow-up studies. Being born with a genital malformation can be a sensitive issue. One may fear that it would be intrusive to ask these persons intimate questions about personality, cognitive function, and sexual matters, and not least to bring up the sensitive subject of atypical sex development. However, some of the individuals affected are of the view that they are constantly aware of these issues anyway, and that it even may be a relief to talk openly about them, and learning more about their diagnosis.

The questions included in the questionnaire concerned very personal matters. To protect each participants' personal integrity, all correspondence was done with neutral envelopes, neutral titles in email conversations, and all send-outs were de-identified and replaced with a study number. All data were collected on this study number, and the code key was kept locked up.

With all participants fully informed and all necessary precautions taken, the risk of violation of the participants' integrity was considered small and the benefit of the knowledge gained large.

The Regional Ethical Review Board in Stockholm approved all studies in this thesis, with ethical permission numbers 2008/1671-31/3 and 2012/1254-32.

4 RESULTS

4.1 STUDY I

Genital measures

Patients were found to have a shorter median penile length compared with controls (10 vs. 11 cm) and also a smaller circumference. Patients with proximal hypospadias also had a shorter penile length compared with more distal cases and controls. The median measured glanular length as well as the distance between corona and meatus was shorter in patients than controls (**Table 4**). The meatus was placed on the tip of the glans in 6.7% of the patients compared with 95.7% of the controls. Glanular sensibility, assessed with a cotton swab compared with the sensibility of the inner thigh, was not affected by the presence of foreskin nor by the number of surgical procedures.

Measures (cm) (Md, (SD))	**Patients**	**Controls**	***P*-Value**
Penile length	10 (2.0)	11 (1.9)	**<0.001**
Penile circumference	10 (2.0)	11 (1.2)	**0.03**
Glanular length	2 (0.7)	3 (0.6)	**<0.001**
Distance corona- meatus	0 (1.0)	1 (0.0)	**<0.001**

Table 4. Genital measures.

Urinary function

Patients presented with more voiding dysfunction symptoms than controls. They also had a lower maximum urinary flow rate (18.8 ml/s vs. 26.2 ml/s, p=0.001), with patients with proximal hypospadias presenting with the lowest flow rates (p=0.036).

Satisfaction with the cosmetic outcome and body esteem

Patients were less satisfied with the cosmetic result, according to PPS, compared with controls concerning penile length, meatal shape and position, glanular shape and general appearance. The total PPS was lower in patients, with differences also between different phenotypes, with the lowest scores in more proximal cases of hypospadias. Only 56% of the patients scored more than 8 points compared with 93% of the controls (**Figure18**).

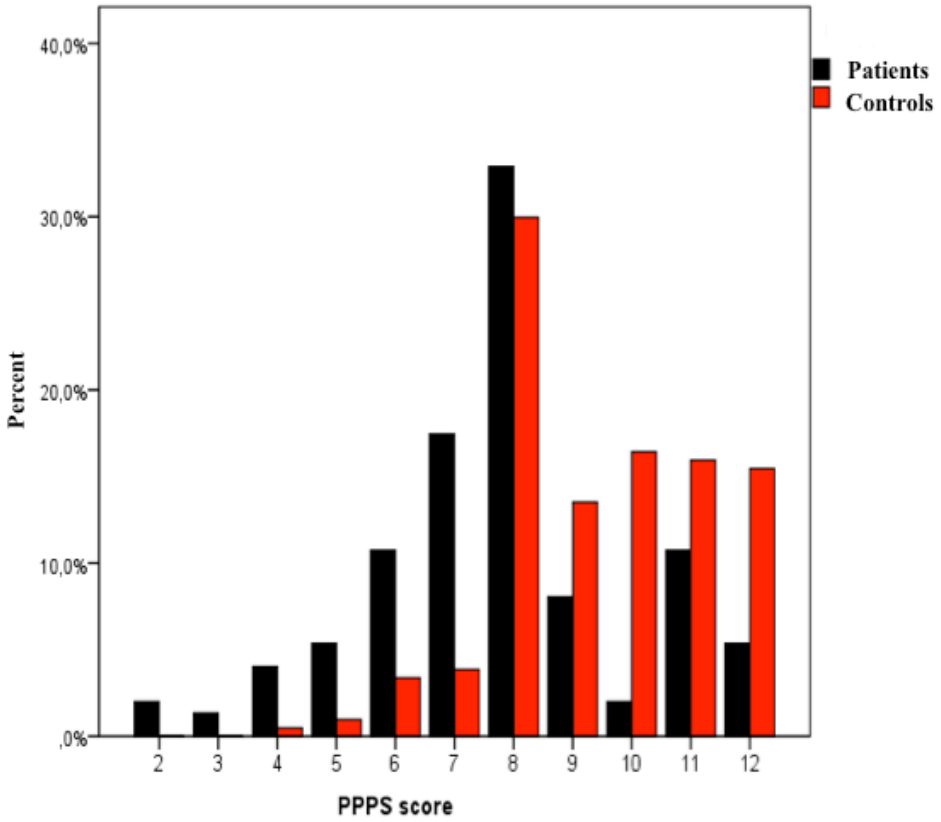


Figure 18. Total PPS in patients and controls.

There were no differences in body esteem according to BES between patients and controls, and the satisfaction with the penile cosmetic result did not correlate with a person's body esteem.

4.2 STUDY II

Patients and controls had a comparable social situation concerning family constitution and working situation. Patients were found to live at home with their parents to a higher extent (p=0.001) and had a lower level of education (p=0.004). In the group with patients with proximal hypospadias, body height was significantly shorter than in controls (p=0.03). Patients had a higher interest in motor sports and a lower interest in cultural activities as adolescents compared with controls.

Quality of life

Total quality of life according to PGWBI was comparable between patients and controls even if patients had lower scores in the sub-scores vitality (p=0.033) and positive wellbeing (p=0.025). There were no differences between different phenotypes.

Childhood experiences

Patients with more proximal hypospadias expressed that they would have liked more medical follow-up as well as psychological support compared with patients with distal hypospadias. Bullying was not reported to a higher extent in patients than in controls, but several comments

about teasing because of the look of the genitals and about how patients avoided "naked situations" show that the problem exists. Regarding attachment patterns, no significant differences were found, but patients with proximal hypospadias more often choose the attachment pattern characterized by avoidance, with a desire to come close to other people, but avoiding doing so out of fear of being hurt.

4.3 STUDY III

Fertility

Patients and controls had biological children to the same extent, but patients with proximal hypospadias less often had children compared with patients with mid-penile or distal hypospadias (p=0.005) and they also had a lower reported fertility compared with other hypospadias patients and controls (p=0.001 and p=0.002, respectively). Those having children had a comparable number of children, while those not having children, had a comparable wish to have children, and fertility issues were rare.

Sexual function

Sexual interest, experience and age at sexarche were comparable between patients and controls (**Figure 19**). Erection issues were rare, but more patients reported anejaculation, and these patients were all childless.

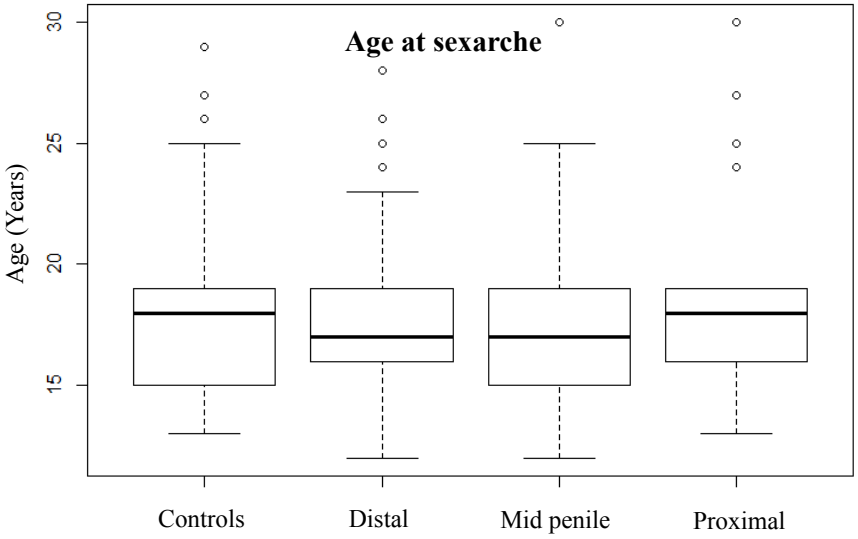


Figure 19. Age at sexarche according to phenotype, compared with controls.

The reported glanular sensitivity was lower in patients and circumcised controls compared with non-circumcised controls (p=0.001). Sensitivity decreased with increased severity (p=0.04) and number of surgical operations (p<0.001).

Eighty percent and 83% of patients and controls, respectively, were satisfied with their sexual life. There were no statistically significant differences between phenotypes, but only 59% of the patients with proximal hypospadias were satisfied. Logistic regression showed that the odds of being satisfied with one's sexual life increased with being in a partnership (OR=8.11, p<0.001) and with a higher PPS (OR=1.54, p=0.01) in patients, but this association was not found among controls. Penile length was not an associating factor. Having proximal hypospadias decreased the odds of being satisfied (OR=0.34, p=0.03). In a multivariate logistic regression analysis justified for phenotype, partnership and PPS, only a higher PPS presented a factor for increased satisfaction (OR=1.57, p=0.02) in patients, but not in controls.

Patients who were not satisfied with their sexual life had a lower median PGWBI score (HRQoL) compared to patients who were satisfied. The difference was not statistically significant, however (p=0.16). In controls, the PGWBI score was similar independently of satisfaction with sexual life.

Further details regarding sexual function can be found in **Table 5**, below.

		Hypospadias	Controls	Distal	Mid penile	Proximal	CC	Chi-square (Fisher's test)
Sexual debut (n (%)	Yes	157 (94)	159 (95)	101 (96)	38 (95)	19 (86)	42 (89)	*NS*
Age sexual debut (y, Mn, SD)		17.8 (3.4)	17.8 (3.1)	17.8 (3)	17.3 (3.8)	19.1 (4.7)	17 (2.4)	*NS*
Erection (n (%)	*Yes*	159 (95)	162 (96)	100 (95)	38(95)	21 (95)	42 (89)	*NS*
	Yes, sometimes	7 (4)	6 (4)	4 (4)	2 (5)	1 (5)	5 (11)	*NS*
	No	1 (1)	0 (1)	1 (1)	0 (0)	0 (0)	0 (0)	*NS*
Satisfaction with erection (n (%))	*Yes*	134 (83)	119 (92)	88 (87)	30 (77)	16 (76)	11 (85)	*NS*
	Quite/to a degree	16 (10)	5 (4)	9 (9)	4 (10)	3 (14)	2 (15)	*NS*
	No	9 (6)	5 (4)	4 (4)	4 (10)	1 (5)	0 (0)	*NS*
	Don't know	2 (1)	0 (0)	0 (0)	1 (3)	1 (5)	0 (0)	*NS*
Ejaculation (n (%))	*Yes*	**152 (93)**	167 (99)	100 (98)	**32 (80)**	20 (91)	43 (93)	*0.002* 0.01***
	No	6 (4)	0 (0)	1 (1)	3 (8)	2 (9)	1 (2)	
	Don't know	6 (4)	1 (1)	1 (1)	5 (12)	0 (0)	2 (4)	
Impotence problems (n (%))	*Yes*	8 (5)	13 (8)	7 (7)	1 (2.5)	0 (0)	4 (9)	*NS*
	No	152 (92)	153 (91)	94 (90)	36 (90)	22 (100)	41 (87)	*NS*
	Don't know	6 (4)	2 (1)	3 (3)	3 (7.5)	0 (0)	2 (4)	*NS*
Satisfaction with sexual life (n (%))	*Yes*	130 (80)	137 (83)	85 (81)	32 (80)	13 (59)	**28 (62)**	*0.016****
	No	33 (20)	29 (17)	17 (16)	8 (20)	8 (36)	17 (38)	
Satisfaction depending on penile length (cm (SD))	*Yes*	9.7 (2.4)	11.7 (1.9)					*NS*****
	No	9.6 (1.8)	11.1 (1.9)					*NS*
Satisfaction depending on PPS (PPS score (SD))	*Yes*	**5.6** (1.8)	7.4 (1.3)					*0.035*****
	No	**4.0** (2.1)	7.0 (1.8)					
Number of sexual partners (n (%))	*0*	8 (5)	8 (5)	3 (3)	3 (9)	2 (10)	4 (9)	*NS*
	1-4	64 (42)	67 (40)	40 (40)	12 (34)	12 (57)	14 (32)	*NS*
	5-10	37 (24)	38 (23)	24 (24)	11 (31)	2 (10)	14 (32)	*NS*
	11-20	14 (9)	19 (11)	9 (9)	2 (6)	3 (14)	3 (7)	*NS*
	>20	33 (21)	36 (21)	24 (24)	7 (2)	2 (10)	9 (20)	*NS*

Mn=Mean, y= years, n= number, SD=standard deviation
PPS= penile perception score
** Patients vs. general controls*
*** Moderate phenotype vs. other phenotypes*
****CC control group vs. patients and controls*
**** Mann-Whithney U test (two-sided)

Table 5. Results on sexual function.

Negative influence

The negative influence of hypospadias on relationships with partners and sexual life was low in the majority of patients. However, among the free comments concerning this matter, several negative issues were described. A low self-confidence, dissatisfaction with the cosmetic genital result or fear of rejection were mentioned as causes for avoiding intimate relationships or not wanting to have sexual intercourse.

Gender development

Core gender identity, gender role behaviour and sexual orientation were sex-typical in both patients and controls. Patients with proximal hypospadias had a lower satisfaction with the assigned sex ($p=0.02$) and a less sex-typical behaviour compared with men with distal hypospadias ($p=0.04$).

4.4 STUDY IV

ASRS

There were no differences between patients and controls scoring ≥ 4 points, which is a cut-off point indicating symptoms of ADHD. Additionally, there were no differences between different phenotype groups.

CPRS-S-A

There were no statistically significant differences between patients and controls, nor between different phenotype groups concerning self-rated depression, anxiety or compulsive disorder symptoms.

MINI

The mean age of the patients who underwent a psychiatric screening was 34.4 (SD 7.1) years and for the controls 27.2 (6.7) years (<0.001). Current or previous psychiatric symptoms were reported in 21% in both patients and controls (**Table 6**). The distribution of symptoms in different phenotype groups did not differ significantly.

Table 6. Psychiatric symptoms at any time in life, according to MINI in hypospadias and controls

	Cases n=33	**Controls n=47**	*p*
At least one psychiatric disorder (n, %)	7 (21)	10 (21)	NS*
At least two psychiatric disorders (n, %)	5 (15)	5 (11)	NS***
Number of symptoms (mean (SD))	0.76 (1.8)	0.49 (1.4)	0.478**
At least one mood disorder (n, %)	5 (15)	5 (11)	NS***
Major depressive disorder (n, %)	5 (15)	2 (4)	NS***
At least one anxiety disorder (n, %)	4 (12)	4 (9)	NS***
Addictive disorder (n, %)	2 (6)	5 (11)	NS***
Psychotic disorder (n, %)	1 (3)	1 (2)	NS***

*Chi-square tests

** Mann-Whitney U test

***Fisher's exact test

Significance level: p≤0.05

5 DISCUSSION

5.1 DISCUSSION ON FINDINGS

The importance of the initial phenotype

Throughout the whole process of this thesis, a pattern has developed. Men who were born with distal hypospadias, and sometimes also mid-penile hypospadias, showed no or small differences compared with controls, and were generally satisfied with the result, while patients with proximal hypospadias differed more often from the controls and were less satisfied with the cosmetic result. Patients with distal hypospadias had comparable genital measures to controls, and were, even if less satisfied than controls more satisfied with the cosmetic result than patients with more proximal hypospadias in *Study I,* while patients with proximal hypospadias presented with more surgical complications as fistulas, a shorter penile length, lower cosmetic satisfaction and a lower maximum urinary flow rate. Patients with mid-penile and proximal hypospadias had had a larger need for and desired more medical and psychological follow-up as found in *Study II*. In *Study III*, patients with proximal hypospadias had a lower reported fertility than other patients and controls and the odds for being satisfied with their sexual life was lower for this phenotype, while patients with distal hypospadias were comparable to controls regarding both fertility and sexual function.

In summary, men born with distal hypospadias seem to have few long-term consequences, which could indicate that hypospadias care has improved, compared with earlier published results [60,70,85]. On the other hand, men born with proximal hypospadias are still less satisfied and have a worse long-term outcome. As one of the largest long-term follow-up studies with patients of different phenotypes, these results contribute to the understanding of the importance of an adapted care and follow-up based on the fact that patients with more proximal hypospadias are in need of more follow-up and support than patients with more distal hypospadias.

Cosmetic result and penile length

Successive generations of young adults seem to continue to raise the bar for what will be deemed a “good cosmetic outcome” making the challenge of hypospadias surgery and the importance of assessment of the result even greater[31]. The evaluation of the cosmetic result after hypospadias repair has over the last few years taken an important place in the long-term follow-up after hypospadias surgery. Reports on negative genital appraisal were published already in the eighties[60,70], and several other publications have followed describing relationships between negative genital appraisal and both psychosocial and psychosexual impaired outcome[44,46,50,57,63,92,108-110]. Objective evaluation of the surgical result is especially important as feedback for the surgeons, for comparison of different surgical techniques, and as an indicator for improved surgical development. However, an objective scoring system like HOSE, based on a satisfactory functional and aesthetic outcome, could be used by both the parents or patient and the surgeon before and after surgery[54]. If the patient or parents are dissatisfied with the result after surgery, the pre-surgical and post-surgical evaluation could improve the dialogue between all

involved parties, and also in the case of referral. HOSE is part of the prospective follow-up of all patients with hypospadias in our hospital today.

The satisfaction with the objective cosmetic outcome, measured with PPS in our study, also has an important influence on several aspects in life. Patients in all three phenotype groups expressed a lower satisfaction with the cosmetic result compared with controls in *Study I*. Free comments made by the patients in *Study II* concerned several aspects of the negative impact of "looking different" in social situations. The study did not show any differences between patients and controls in the experience of having been bullied. Bullying and teasing are however common, and a study of American university students showed that 10% had been teased about their penile appearance, mostly because of penile size, but also because of a "strange" penile appearance and 47% had witnessed someone else being teased, strengthening the surgical aim of a satisfactory cosmetic result[111].

The odds of being satisfied with their sexual life was higher if a patient was satisfied with the cosmetic result as shown in *Study III*. This relation was not found in controls. Even if patients, especially with mid-penile and proximal hypospadias, were less satisfied with penile length than controls, the satisfaction with their sexual life was not associated with penile length either in patients or in controls. Thus, even if penile length is important for the satisfaction with the cosmetic result, it seems more important with an overall satisfaction with the cosmetic result for the sexual outcome. Since penile length augmentation remains a surgical challenge, this is reassuring.

The consequences of a negative genital appraisal could be of great importance. To be able to determine the relationship between psychosocial and psychosexual outcomes and the patients' subjective perceptions of themselves in relation to their perceived norms, further instruments would need to be developed. A patient's regard and appraisal of the cosmetic genital result do probably not only depend on the actual surgical outcome, but can be hypothesized as being related to the person's own referral points and coping mechanisms. It would therefore be of help to develop realistic patient and parental cosmetic expectations with pre- and postoperative guidance[31]. The parents will be the patient's major source of reference when he reaches adolescence and therefore the parental attitudes towards the resulting penile appearance and the condition are important. It is also important to reassure the patient postoperatively, or later on at an appropriate age, about the normality of his penis, especially with regard to penile size and an eventual absence of foreskin. With more knowledge, the risk of developing a sense of shame and suffering social embarrassment is lower. Tools for both parents and patients on how to cope with a genital malformation are therefore an important part of the care of these patients.

Circumcision and glanular sensitivity

The reported glanular sensitivity in our study is a subjective measurement. In *Study I*, the participants coming to the outpatient clinic were asked to compare the sensed effect of a cotton swab touching the inner thigh and the glans on a 4-level scale. No differences were found between patients and controls. In *Study II*, the experienced sensitivity was reported on a VAS-

scale from 0-10, and patients and circumcised controls reported a significantly lower sensitivity compared with non-circumcised controls. The reference point is for natural reasons the reporting person himself. Many studies have been published on glanular sensitivity comparing circumcised men with not circumcised men with varying results, with both subjective and more objective ways of measurement, but generally no real differences were found in sensitivity between circumcised and non-circumcised men[112-116]. The reported sensitivity in our study was lower both in patients and circumcised controls compared with uncircumcised controls in *Study II*. Hypospadias surgery can have an impact on the sensitivity in another way than the absence of foreskin, since scarring on the glans may also affect the sensitivity. In Sweden, where circumcision is not routinely performed, a circumcised penis may be considered as "different-looking", which several patients commented on. In *Study I*, circumcised hypospadias patients and controls circumcised because of phimosis wished to a higher extent to have their foreskin intact than controls circumcised for cultural reasons. Thus, independent of the impact of the lack of foreskin on sensitivity, it is important to take the local culture concerning circumcision into consideration to avoid the feeling of abnormality[61].

Psychosocial situation

Patients with hypospadias were found to have a psychosocial situation comparable with controls and a good quality of life. The finding in *Study II* of patients having a lower level of education compared with controls is in line with the results of Berg et al.[60]. The level of education among patients was, however, above the level of the Swedish population, and Sandberg et al. did not find this difference[82]. To avoid the impact of persons with higher levels of education choosing to participate as controls, a register-based study may be more appropriate to assess educational level.

Patients with proximal hypospadias were found to have a shorter stature than controls as found in *Study II.* However, even if short stature could potentially induce psychosocial stress, previous research has shown that there are no effects on psychosocial adaption regarding individuals who only are shorter than average and otherwise healthy[117]. Nevertheless, it can be hypothesized that short stature with concomitant hypospadias may add to the feeling of looking different and might reflect the impact of early growth restriction as a cause of hypospadias.

Health related quality of life in adult men with corrected hypospadias has been scarcely studied, but the results in *Study II* indicating comparable levels of HRQoL, was also found in another study comparing adult men with corrected hypospadias with circumcised controls[92,110]. The differences in vitality and positive well-being in our study are interesting and further qualitative studies could give us more information on the matter. Even if this study represents one of the largest in the field with different phenotypes of hypospadias, no statistically significant differences were found between different phenotype groups. If there are differences to be found, they are probably minor, demanding larger groups of patients to increase power.

The diagnosis of hypospadias may cause large amounts of stress for the parents when their baby is born. Parents to children born with an unknown sex and parents to children with DSD have

shown high rates of post traumatic stress[118]. This may affect their ability to bond with their child. To avoid a negative impact on the ability to bond, early information by a urologist and psychological support, when needed, for the parents is important. We could not show any significant differences in attachment patterns in *Study II* between patients and controls. However, the patients with proximal hypospadias tended to choose an avoidant attachment style to a higher extent compared with other phenotypes. No earlier studies have been done on this matter to our knowledge, but it would be of interest to perform the same assessment with a larger group of patients with proximal hypospadias added by qualitative studies. The patient's either positive or negative self-appraisal is also important, since it influences his ability to dare to attach to other people. To help the child/ adolescent to feel that he is worthy of other people's friendship and care is therefore of great importance, and the medical team need to be prepared to offer psychological support, e.g. psychoeducation about coping strategies. However, further research is needed to elucidate self-image and parental stress in hypospadias.

Fertility

The reported fertility was found to be lower in the group with patients with proximal hypospadias compared with other patients and controls, but comparable between the total group of patients and controls. A reduced fertility rate can be due to the underlying cause of hypospadias, an impaired sperm quality, additional genital disorders such as undescended testes, urethral dysmotility, anejaculation, sexual dysfunction or psychosocial factors. Only one published study has so far performed sperm analysis in patients with hypospadias, reporting lower fertility in spite of normal semen parameters[65]. With only 3% of the 112 men participating in the above mentioned study having scrotal hypospadias, conclusions concerning different phenotypes are not possible. Further studies on the matter would be of great interest. Even if the majority of all men with hypospadias have a normal fertility, it is important to screen for the need of further assistance since assisted reproduction may be of great benefit[119].

However, fertility of a person is not only influenced by anatomical and medical aspects, but also by psychosocial factors. To dare to initiate intimate relationships is crucial, and body acceptance is of great importance. The need of continuous psychological follow-up and support needs to be evaluated in each patient. Psychosocial reasons causing reduced fertility rates are more difficult to assess, but qualitative studies could add more knowledge.

Sexual function and psychosexual outcomes

A satisfactory sexual function is one of the objectives of hypospadias surgery, and an important factor for a good HRQoL. The long-term outcome concerning sexual function has been assessed in several studies, but studies performed with adequate controls and validated measures are scarce[61,120-123]. In *Study III*, patients with hypospadias were found to have a sexual activity and interest corresponding to controls, as well as the same number of sexual partners and the same age at sexarche, findings also confirmed by e.g. Aho et al. and Moriya et al.[46,61].These results can contribute to provide reassuring information to the patients, which is important. There are, beyond the surgical result and anatomic genital features, psychological aspects that are probably

even more important for a satisfactory sexual life. Even if the satisfaction with sexual life was comparable in patients and controls, the odds of being satisfied with sexual life was higher in patients if the cosmetic satisfaction was higher, again imposing the importance of the cosmetic result. According to our results, the impact on HRQoL of being satisfied with your sexual life seems more important in patients than in controls. As with the satisfaction with the cosmetic result, coping mechanisms play an important role, and during the clinical follow-up in adolescence, a tool for finding those patients in need of more support would be of great value.

The hypothesized differences in gender development in men with hypospadias could be expected to be smaller than in the group with women with CAH for example, since the majority of patients with hypospadias have a normal androgen metabolism and no other known cause of their hypospadias. We could not show any differences in *Study III* between patients with hypospadias and controls in gender identity, gender role behaviour or sexual orientation. A few and small studies on this matter have resulted in varying inconclusive results[72-75]. One study investigated gender role behaviour in 19 boys with hypospadias (ages: 3-7 years) compared with unaffected boys showing no atypical gender role behaviour, consistent with another study of 175 boys with hypospadias (ages 6-10 years), while Berg et al. found a more uncertain gender identity in 34 adult men but a comparable sexual orientation[72,74,75]. In our study, patients with proximal hypospadias, however, showed a lower satisfaction with the assigned sex and a less sex-typical behaviour compared with men with distal hypospadias. No earlier studies, to our knowledge, have analysed gender development depending on different phenotypes of hypospadias, which is why these results are interesting. The differences were small, however, and the question needs to be studied further to be able to draw any conclusions.

Our results concerning sexual function and psychosexual outcome are important and reassuring, and the age-matched controls provide value to the study. Prospective studies on these patients with validated questionnaires, which could be integrated into the regular clinical follow-up starting during early adolescence and then continue up to adult age, would add more knowledge to the subject and also enhance the chances of a good participation rate and a high scientific quality.

Psychiatric outcome

The psychological outcome in men born with hypospadias has been studied, mostly in the eighties, with limited number of subjects and with varying results. The hypospadias in itself, as well as the surgical procedure, hospitalization, and adverse cosmetic outcomes have been hypothesized to cause adverse psychological effects. In *Study IV,* we clinically investigated the prevalence of symptoms of ADHD, anxiety, depression and compulsive-obsessive disorders and performed a psychiatric screening, finding no differences between patients and controls. This confirms the findings of Mureau et al. who also performed a questionnaire study investigating the psychosocial functioning of both children, adolescents, and adults following hypospadias surgery, finding comparable results between patients and controls regarding behavioural/emotional problems including e.g. anxiety, depression and attention problems[79]. They did not investigate

psychiatric symptomatology, however, which is scarcely investigated. Register-based studies have found an increased prevalence of intellectual disability, autism spectrum disorders (ASD), ADHD and behavioural/emotional disorders compared with controls as well as an increased risk for ASD in their brothers, proposing a common familial genetic/environmental background[98]. Since an increased risk for neurodevelopmental disorders has been identified, further clinical investigation with larger groups of patients and controls could bring more light to the issue.

With the treatment modalities used today, including earlier surgery, better surgical techniques and shorter hospital stays, new assessments would hopefully show results with less negative impact from the treatment, which is why a continued follow-up is important.

5.2 DISCUSSION ON METHODOLOGY

Limitations or possible errors exist in all studies. The reliability and importance of a study depends on its internal and external validity. The internal validity, meaning if the study is measuring what the study is supposed to measure, is important for the *external validity* of a study, meaning the generalizability of the results of the study to another population. The precision of a study is a function of random errors in the measurements in the study, which is inevitable. In statistical test theory, there may be statistical errors in the hypothesis testing distinguished as type I and type II errors. Type I errors occur when a null hypothesis (H_0) is true but is rejected, "a false positive". With a significance level (α) of 0.05 (5%) we accept that we have a 5% probability of incorrectly rejecting the null hypothesis. Type II errors occur when the null hypothesis is false, but is not rejected, a "false-negative". The rate of the type II error is noted β and is related to the power of a test. Insufficient statistical power is possible in our study, especially in analyses on different phenotype groups. Even if our study is one of the largest in the field and with patients from two of four national centres, the group with patients with proximal hypospadias will always present a smaller number of individuals, which is why multicentre studies are of great importance to enhance power and avoid type II errors.

Internal validity

The internal validity may be affected by systematic errors. Systematic errors are classified into selection bias, misclassification and confounding.

Selection bias

The study subjects in this thesis are all members of a cohort sample. A *selection bias* may be introduced if the association between the outcome and the exposure differs between those who participate and those who do not and may be caused by several factors. The willingness to participate depends on factors influencing the interest of participating in a follow-up study such as self-interest or interest in scientific progress. The selection can turn both ways; satisfied patients without any problems may want to participate to express their satisfaction, and the contrary is true of dissatisfied patients. Individuals with a higher level of education have also been shown to participate more often in studies, which might have had an influence on the results

on educational level as described in *Study II*[124]. The best way to handle selection bias is to perform a randomized control trial, which is, however, not an option when investigating a retrospective cohort. The participation rate in our study was low but it corresponds to the majority of the other studies in the field, since it is a common problem in long-term follow-up studies. Contrary to other diseases, which include a life-long follow-up and treatment, the majority of the patients with hypospadias have surgery at an early age, followed by clinical control, but are thereafter "cured". The incitement to participate in a follow-up study, many years after this, may therefore seem low for these patients. Prospective studies including patients from the beginning for follow-up until young adult age may enhance the participation rate. The study population also depends on the availability of addresses for all patients, the presence of a computer or at least literacy and a level of comprehension, factors that influence the *coverage for sampling*. The percentage fulfilling the participation depends on the construction of the questionnaire and patience and an ability to concentrate is needed. In *Study IV*, concerning the questions about psychiatric symptoms, this could have presented a selection bias, resulting in a more positive outcome if participants with e.g. ADHD did not have the ability to concentrate to complete the questionnaire. Questions concerning sensitive matters may lead to increased item non-responses, but can be, at least partly, avoided using self-completion administration and the assurance of the anonymity of the participant is of great importance. In our study, the response rate was high. Our patients that came to the clinic for a psychiatric screening were significantly older than the controls, but since MINI screens for both current and historical symptoms, this enhances the results, since the patients would have been expected to acquire psychiatric symptoms with increasing age.

Misclassification

When information on the outcome or exposure is wrong, misclassification or information bias is introduced. Depending on whether the misclassification depends on the person's status or not, it is classified as differential or non-differential. To avoid misclassification in our study, the information concerning the used surgical technique was not used as exposure, since the patient charts were not complete. Differential misclassification may be introduced if an interviewer knows if the subject is a case or a control and could affect the result to be weaker or stronger. The interviewers performing MINI were unaware therefore of the subject's statuses. Questionnaires present a standardized similar protocol for both patients and controls, which is why this issue is avoided. Self-assessment questionnaires also minimize the *social desirability bias* compared with face-to-face interviews, that is the desire of respondents to present themselves in the best possible light[125]. Another type of bias in questionnaires is caused by the *response-choice order.* In self-completing questionnaires, the respondent has a tendency to choose the first choice, a primacy effect, while in face-to-face interviews, the respondent tends to begin processing the final alternative since it was the last to be presented; a recency effect. These two present non-differential misclassifications. To minimize the risk of information bias, a CRF was constructed for the clinical exams with detailed written instructions on how to measure each genital measure, group discussions with the examiners before the study started to make sure everyone was doing the same thing, and a limited number of examiners.

Confounding

To evaluate if the internal validity is good in this study we had to ask ourselves if there may have been alternative cause or causes, confounding factors, which explains the observations and results we have found. Possible confounders in our study, for example, are the phenotype of hypospadias and a history of genital surgery (**Figure 20**).

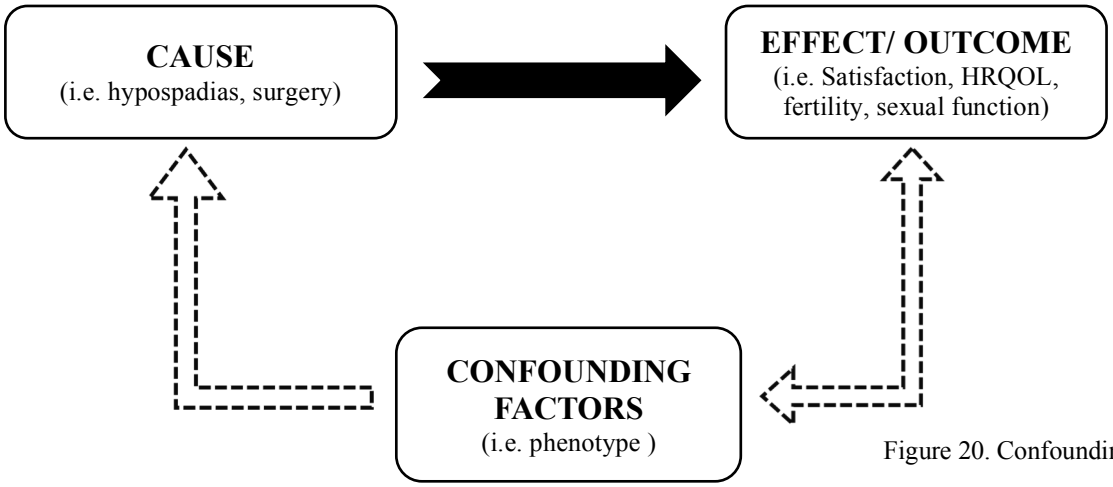


Figure 20. Confounding factors.

To approach the problem of confounding, an age-matched control group was selected, and also a control group having had surgery for phimosis. During data analysis, stratification was performed and the analyses were adjusted for possible confounders when necessary.

External validity

External validity is the extent to which it is possible to generalize results from one study population to other situations and populations. A low response rate, which is often a problem in questionnaire studies and long-term follow-up studies, may affect this reliability[125]. A drop-out analysis tests whether the respondents differ to a large extent compared with the non-respondents and main characteristics of the study group were not significantly different from those of the initial population.

Our results were not analysed according to the used surgical method as mentioned above, since this information was incomplete in the patient charts. Therefore our results are not reporting the outcome of a certain surgical technique, but the long-term outcome of being born with hypospadias and having undergone genital surgery. Ethnicity may have an impact on the external validity since different cultures come with different traditions. Concerning the wish to preserve the foreskin expressed by patients in our study, this is probably an opinion based on our tradition in Sweden to preserve boys' foreskins. The care of patients with hypospadias has improved over the years; both concerning surgical techniques, but also the perioperative care has improved due to e.g. shorter hospital stays, better stents and antibiotic regimes. Our results, therefore, may not completely reflect the outcome of the boys being born with hypospadias today, but represents a level from where even better results may be expected in the future.

Questionnaire and clinical studies

Several aspects of pursuing questionnaire studies as well as clinical studies may affect the accuracy and quality of the data obtained. Administration issues, such as the mode of contacting respondents, the mode of delivery of the questionnaire, as well as the way the questions are administered are of great importance[125].

Strengths

Questionnaires allow obtaining quantitative data, for a relatively low cost and short time, about people's attitudes, values, experiences and past behaviour. If administered by email, they may even enhance the flexibility for the participant[126]. The collected data may be analysed scientifically and objectively and the results of validated questionnaires can be compared with earlier research and measure change[106]. In a cross-sectional follow-up study such as ours, questionnaire studies present the best method to study long-term outcome, and may also be used to suggest a hypothesis for further prospective cohort studies. Little research has been done comparing different self-administration modes, but only small differences have been shown between self-administered paper questionnaires and self- administered electronic questionnaires concerning response patterns[125]. Computer-assisted self-completed questionnaires have led to fewer missing item responses however. A greater anonymity, as in postal and electronic administered questionnaires, has shown to lead to a higher item response and more accurate reporting in sensitive matters, even if face-to-face interviews have a lower item non-response in general. In this case, with a number of questions concerning intimate matters, such as sexual preferences and interest, a self-completion questionnaire was more appropriate.

Limitations

One of the main limitations of questionnaire studies is the low response rate. In combination with missing or improperly completed answers, the number of useable questionnaires may be low. Of those accepting participation in our study, the response rate was high however (85%). In contrast to interview studies, the researcher does not have the opportunity to follow-up the answers given by the responder. An identified difference or trend is not explained by the questionnaire, but may need to be completed by deep interviews. To permit the responders to explain their answers to a certain degree, each section was followed by an open question where responders could add comments. Questions with fixed answers forces the respondent into choosing one of the answers, implying that the responder has knowledge in the matter. Cultural, social and language differences can also influence the interpretation. A question that is misunderstood or not understood may lead to biased or misleading results stressing the importance of the construction of the questions in a questionnaire[126].

Psychosocial outcome in terms of education, work and family situation is influenced by many different factors such as psychosocial background, local culture and place of living. In a questionnaire study these factors may be difficult to adjust for because of a limited size of the sample and lacking data and therefore a register study may be more appropriate. A register study

can, however, not assemble data on free time activities, bullying or quality of life, which is why a combination of these methods is essential.

A register study is based on diagnoses found in a database, which may contain information bias with diagnoses set on the wrong criteria, while a clinical investigation has other weak points. Since all patients and controls had voluntarily chosen to come to our clinic, which requires a certain state of health, this population may be under representative in number of diagnoses compared with the whole patient and control population, as well as with the general population. Recruiting volunteer patients and controls always has the risk of selection bias as those with psychiatric symptomatology may have difficulties participating in a research study. A limited number of participants also limits the possibility to present small differences, which was especially the case in the psychiatric screening.

6 CONCLUSIONS

Study I

Patients with hypospadias presented with more voiding dysfunction and had a lower maximum urinary flow rate than controls. They were also less satisfied with genital appearance and had a shorter penile length. The group with proximal hypospadias were less satisfied with genital appearance and had a shorter penile length than those with more distal hypospadias.

Study II

There was no significant impact on the health related quality of life and patients with hypospadias had a comparable psychosocial life comparable with controls. Patients with proximal hypospadias were shorter than controls and they needed or had been in need of more psychological/sexological support.

Study III

Patients had biological children to the same extent as controls and the reported fertility was comparable between patients and controls. However, patients with proximal hypospadias had a lower reported fertility.

Sexual function was favourable and 80% of both patients and controls were satisfied with their sexual life. In patients, the satisfaction of sexual life depended on the level of genital appraisal, and the odds of being satisfied with sexual life were also lower in patients with proximal hypospadias.

Study IV

Our results do not support an increase in psychiatric morbidity in men with hypospadias.

7 CLINICAL IMPLICATIONS

During my work with this thesis, I have come to feel that this group of patients, comprising a large number of men in our society, are worth more attention. To be born with a genital malformation, which sometimes means several surgical interventions and a genital cosmetic result, which may not resemble other boys', may be difficult. It concerns a sensitive area of the body and not something most boys talk about in school or among friends. The health care system has an important role in informing them that they are not alone, taking care of these patients and their parents, helping them get the best surgical result possible and helping them to live with the result in the best possible way.

Throughout this thesis our understanding of the importance of the phenotype of hypospadias have deepened. In the same way as the aetiology is believed to differ between proximal and distal hypospadias, the outcome also seems to be different. Therefore, the clinical follow-up should be adapted to the needs of the patients.

As in clinical practise today, all patients should be followed initially to ensure that the surgical and urological result is satisfactory. The boys with distal hypospadias could then be followed if needed. The patients with mid-penile and proximal hypospadias need a follow-up at least until puberty with continued support during their upbringing.

With the knowledge that patients with proximal hypospadias have a negatively impaired outcome in several aspects, these men should be offered more psychological and sexological support and also fertility assessment in their mid-teens. The parents, as the patient's major resource of reference during upbringing and adolescence, also need support to construct a positive attitude towards the diagnoses and the genital outcome.

It is important to remember that the paediatric urologist or hypospadias surgeon only see the patient for the first ¼ of the patient's lifetime, or even less. To ensure that the patients with a need of continued follow-up receive the support they need, a system of transitional care must be available. A close cooperation with adult urologists, familiar with the initial hypospadias surgical techniques is of utmost importance, as well as psychological and sexological support. Beyond the patients' perspective, this continued follow-up is also of great value from a research perspective, since long-term follow-ups are our only way to measure our results and make improvements.

8 FUTURE PERSPECTIVES

This thesis has contributed to the understanding of the long-term outcome for men born with hypospadias.

As described in *Study I,* most patients have a satisfactory outcome concerning both surgical and urological results, with a comparable quality of life as shown in *Study II*, a satisfactory psychosexual function and a comparable fertility as described in *Study III,* and no signs of an increased prevalence of psychiatric morbidity, as shown in *Study IV*.

However, there are several research avenues to pursue in the future.

First, questionnaire studies are a good and in some research situations the only way to assess long-term results. To enhance the participation rate and minimize the risk of selection bias, prospective follow-up studies, with the possible inclusion of all patients with hypospadias passing through our medical care system, is necessary to continue to ensure a high quality of the care of these patients. The patients could then be followed with the possibility to assess their outcome both psychosocially and psychosexually until young adult age. Moreover, continued epidemiological studies are an important complement to evaluate psychosocial data such as education, and family and work situation.

Secondly, a standardized way of classifying hypospadias accepted internationally would enable better comparisons and co-operations between different centres. No symptom-specific outcome measure for QoL exists for patients with hypospadias, which is regrettable. The development of a new health measurement scale with good reproducibility and validity is a challenge and requires considerable investment, but an instrument focusing on the important issues after surgery in men with hypospadias, such as emotional aspects and lower urinary tract symptoms would be of great importance in the follow-up of these patients. This instrument could be combined with one of the existing measures of genital appraisal and assessment of sexual function. The DISF-SR measure assessing sexual function was not applied in this study, but should make an appropriate complement in a future follow-up of our adolescent patients with hypospadias.

Thirdly, the reported fertility in men born with proximal hypospadias was lower compared with other patients. This needs to be further investigated in a larger material and with sperm analyses. A multicentre study could provide the needed number of patients. Qualitative research studies with structured interviews could also provide more information on this sub-group of patients as to why their outcome is more impaired.

Finally, while this thesis provides some clues concerning how men born with hypospadias are affected by their diagnosis during their lives, further research is needed. As surgeons and health care givers, we have a responsibility to continue to assess the quality of the surgery performed as well as the follow-up provided, and to continue to give the best possible care based on the current evidence-based knowledge we have.

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The mystery of nature; we are all unique.

Fossils from Gotland. Photo by Anna Hemph.

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11 APPENDICES

A. The complete questionnaire – patient version. Included instruments with copy write are not included, but marked with names. All questions are not included in this thesis.

B. The Case report form

Appendix A. The complete questionnaire – patient version. Included instruments with copy write are not included, but marked with names.

Kodnr	

Frågeformulär för uppföljning av hypospadi

Vi utför en långtidsuppföljning av män som opererats för hypospadi och adresserar därför denna enkät till dig då vi via journaler har fått uppgiften att du opererats på grund av detta. Syftet med undersökningen är att få en bild av hur hypospadibehandlingen (särskilt den operativa med efterföljande läkarbesök) har påverkat barndomen och det vuxna samlivet, både psykiskt och fysiskt för att kunna optimera omhändertagandet av denna diagnos.

Kort bakgrund om hypospadi: Hypospadi är vanligt hos pojkar (ca 1 av 300 nyfödda pojkar) och innebär att urinröret är för kort och mynnar under ollonet, på penisskaftet, i pungen eller under pungen i själva bäckenbotten. Operationer görs ofta för att förlänga urinröret så att det går bättre att kissa rakt fram samt av kosmetiska skäl. Ibland ligger penis böjd nedåt vilket kan försvåra samlag. Detta korrigeras också vid urinrörsoperationen. Operationsmetoderna har varierat genom åren liksom operationstidpunkt och efterföljande kontroller. Milda former behöver ofta ingen uppföljning medan de mest uttalade kan behöva opereras flera gånger och kontrolleras under flera år.

Svaren på frågorna behandlas anonymt.

Resultaten kommer att sammanställas och presenteras i vetenskapliga tidskrifter.

Har du frågor kring denna undersökning, eller om du känner att du skulle vilja komma i kontakt med vården med tanke på eventuella aktuella problem kan du kontakta oss på telefonnummer 073-655 20 95/ 08-517 77228 (Lisa Örtqvist) alternativt mail: hypospadi@gmail.com.

Frågorna som besvaras med ett värde på en skala är rekommenderade för att de ska vara möjliga att analysera, övriga frågor är helt frivilliga.
Om du tycker vissa frågor är för känsliga eller svåra att besvara kan du avstå från att svara på dessa.
Du ingår i en liten grupp av patienter, som vi slumpmässigt valt ut bland vårt stora patientmaterial, som får testa denna enkät först. Vi är därför mycket tacksamma om du i slutet av enkäten skriver hur det var att delta i denna undersökning och om det är något du speciellt tänkte på när du svarade på enkäten.

1. Civilstånd:

- ☐ Gift/Sambo
- ☐ Ensamboende med fast relation
- ☐ Ensamboende utan fast relation
- ☐ Annat, ange gärna vilket:_____

2. Har du syskon?

- ☐ Ja, Antal: ☐ st
- ☐ Nej

3. Vad har du för sysselsättning?

- ☐ Yrkesverksam
- ☐ Sjukskriven
- ☐ Studerar
- ☐ Arbetslös
- ☐ Pensionär
- ☐ Annat, ange gärna vilket:_____

4. Utbildning: Den här frågan handlar om den utbildning du har. Du kan svara ja på flera utbildningsnivåer.

		Avklarad examen	Inriktning
☐	Grundskola	☐	
☐	Gymnasium	☐	
☐	Högskola/universitet	☐	
☐	Annat	☐	

5. Fritidsintressen: Denna fråga handlar om vad du gör på fritiden, både när du var tonåring och idag.

Under tonåren: _____

_____

Nuvarande: _____

_____

6. Barndomen: Dessa frågor handlar om de aktiviteter och lekkamrater du föredrog som barn. Välj och ringa in, för varje fråga, det alternativ som bäst beskriver vad du tyckte om i barndomen.
Questionnaire concerning gender development, not included because of copywrite reasons.

7. Om du tyckte om sport, vilka sporter tyckte du om då?

_____
_____

6. Vikt: Hur mycket väger du? ____ kg

7. Längd: Hur lång är du? ____ cm

8. Röker Du?
- ☐ Ja, röker regelbundet — paket/v sedan ___ år
- ☐ Ja, då och då/Feströker — pkt/mån sedan ___år
- ☐ Nej

9. Finns någon annan i din släkt som har hypospadi?
- ☐ Ja
- ☐ Nej

Om ja, hur är denna/dessa person(er) släkt med dig?

_____
_____

10. Är du född i Sverige?
- ☐ Ja
- ☐ Nej

Om nej, i vilket land är du född?

_____
_____

11. Är dina föräldrar födda i Sverige?
- ☐ Ja, båda
- ☐ Ja, mamma
- ☐ Ja, pappa
- ☐ Nej, ingen av dem

Om någon eller båda dina föräldrar är födda utanför Sverige, i vilket land är de födda?

_____
_____

12. Ingår det barn i din familj (biologiska barn, adopterade barn och bonusbarn)?
- ☐ Ja
- ☐ Nej

Om ja,
Hur många barn har du? Hur gamla är de? Vilket kön är de?
Är de biologiska, adopterade eller bonusbarn?

_____

_____

13. Om du INTE har barn, vill du ha barn?
- ☐ Ja
- ☐ Nej
- ☐ Vet inte

14. Har din nuvarande eller tidigare partner varit
- ☐ Ja

gravid med dig?

- ☐ Nej
- ☐ Vet inte

15. Har du försökt få barn?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

16. Har du haft svårt att få barn?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Frågor om information

17. Har du fått information om din hypospadi från sjukvården?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om ja,
Hur gammal var du när du fick information om din hypospadi från sjukvården? _____
Kommer du ihåg vad du fick reda på?

_____
_____
_____

Tycker du att den information du fick var tillräcklig?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om du inte tycker den var tillräcklig, kan du beskriva varför?

_____
_____
_____

19. Har du fått information om din hypospadi från dina föräldrar?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om ja,
Hur gammal var du när du fick information om din hypospadi från dina föräldrar? _____
Kommer du ihåg vad du fick reda på?

_____
_____
_____

Tycker du att den information du fick var tillräcklig?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om du inte tycker den var tillräcklig, kan du beskriva varför?

_____

Frågor rörande operativ behandling

20. Är du opererad för hypospadi?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om ja,
Vilken typ av operation har gjorts? Om du vet namnet på operationen får du gärna skriva det, annars beskriva om möjligt vad som gjorts.

_____
_____
_____
När har operationerna gjorts? _____

21. Hur upplevde du efterkontrollerna hos läkaren? Sätt ett kryss på det värde som motsvarar ditt svar. 1= Negativt 10= Positivt

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

22. Hur upplevde du informationen kring operationen? Sätt ett kryss på det värde som motsvarar ditt svar. 1= Negativt 10= Positivt

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

Har du kommentarer kring den information du fick kring operationen eller om efterkontrollerna hos läkaren?

_____
_____
_____

23. Blev det några komplikationer efter någon operation?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

24. Har du förhuden kvar?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

25. Om du inte har förhuden kvar, har du önskat att du hade det?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Frågor om puberteten

26. När gick du in i pubertet, dvs fick utlösning, målbrottet och fick könshår?

- ☐ Minst 2 år tidigare än jämnåriga
- ☐ 6 månader – 2 år tidigare än jämnåriga
- ☐ Ungefär samtidigt som jämnåriga
- ☐ 6 månader – 2 år senare än jämnåriga
- ☐ Mer än 2 år efter jämnåriga
- ☐ Vet ej

27. Upplever du att hypospadin påverkade din pubertet negativt?
Med "påverkade negativt" menas om den hade en negativ inverkan på din pubertet både kroppsligt och känslomässigt.

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

28. Hur har det påverkat din pubertet?

_____
_____
_____

Frågor om hur hypospadin påverkat dig

29. Har hypospadin påverkat din uppväxt negativt under barndomen (upp till 18 års ålder)?

1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

30. Har hypospadin påverkat din fritid negativt?

1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

31. Har hypospadin påverkat ditt kamratliv negativt?

1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

32. Vänner
Välj det svar som passar bäst för varje påstående.
Questions part of Questionnaire by Hines concerning play behavior, not included for copywrite reasons.

33. Har hypospadin påverkat relationen med dina föräldrar negativt?
1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

34. Har hypospadin påverkat med dina syskon negativt?
1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

35. Har hypospadin påverkat relationen med dina partners negativt?
1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

Om hypospadin har påverkat dina relationer, beskriv gärna hur.
_____
_____
_____

Frågor om andra sjukdomar och besvär

36. Har du haft några andra sjukdomar/besvär tidigare? Vilka?
Med sjukdomar/besvär menar vi fysiska problem som gjort att du mått dåligt och eventuellt behövt uppsöka sjukvård, lett till operation eller behandling av något slag.
_____
_____
_____

37. Har du några andra sjukdomar/besvär nu? Vilka?
_____
_____
_____

38. Har du någon gång varit i kontakt med sjukvården på grund av psykiska besvär?
☐ Ja
☐ Nej
☐

Vet inte

39. Tar du för närvarande några mediciner?
- ☐ Ja
- ☐ Nej
- ☐ Vet inte

40. Har Du opererats för icke nedvandrad testikel?
- ☐ Ja, höger
- ☐ Ja, vänster
- ☐ Ja, båda
- ☐ Nej
- ☐ Vet inte

41. Har du opererats för någon annan medfödd förändring?
Med medfödd förändring menas sådana förändringar som man är född med och som ofta korrigeras kirurgiskt, t.ex ljumskbråck i barndomen eller läpp-gom-spalt.
- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om ja, vilken annan medfödd förändring är du opererad för?

_____
_____

Uppföljning rörande penis

42. Hur nöjd är du med din penis?

PPS Questionnaire, concerning genital appraisal, not included because of copywrite reasons.

43. Om du mätt penis längd, vilket mått har du uppmätt ?

	1-5 cm	6-8 cm	9-10 cm	11-12 cm	13-15 cm	16-17 cm	>17 cm	Vet ej
Under erektion (stånd)	☐	☐	☐	☐	☐	☐	☐	☐
Ej under erektion (slak)	☐	☐	☐	☐	☐	☐	☐	☐

44. Växte din penis under puberteten?

1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

Kommentarer kring hur du tyckte penis förändrades under puberteten:

_____
_____
_____

45. Har du funderat på att söka rådgivning (t.ex. ungdomsmottagning) rörande penis utseende eller funktion?
- ☐ Ja, och jag har sökt rådgivning
- ☐ Ja, men jag har inte sökt rådgivning
- ☐ Nej
- ☐ Vet inte

46. Har du haft besvär med följande saker?	Ja, nu	Ja, någon enstaka gång	Ja, tidigare	Nej	Vet inte
Att det tar lång tid att kissa?	☐	☐	☐	☐	☐
Svårigheter att kissa (t.ex att komma igång/få en bra stråle/smärta/lång tid att kissa)?	☐	☐	☐	☐	☐
Urinläckage?	☐	☐	☐	☐	☐
Urinstråle riktad mycket nedåt?	☐	☐	☐	☐	☐
Urinvägsinfektion?	☐	☐	☐	☐	☐
Fistlar (som ett extra hål där urinen kommer ut, kissar med två strålar)?	☐	☐	☐	☐	☐
Ärrbildning?	☐	☐	☐	☐	☐

47. Har du haft några andra besvär gällande penis eller urinering?

_____

_____

_____

Uppföljning rörande ollonet

Ibland påverkas ollonets känslighet i samband med operation. Därför följer några frågor om ollonet.

48. Hur upplever du ollonets storlek?

- ☐ Lagom
- ☐ För stor
- ☐ För brett
- ☐ För liten
- ☐ Vet inte

49. Är ollonet viktig för lustupplevelsen vid sex?

- ☐ Ja, mycket
- ☐ Ja, delvis
- ☐ Nej
- ☐ Vet inte

50. Hur upplever du ollonets känslighet?

Sätt ett kryss på det värde som motsvarar ditt svar.

1= Okänsligt 5=”Lagom” känsligt 10= Överkänsligt

[---I---I---I---I---I---I---I---I---I---]

1 2 3 4 5 6 7 8 9 10

51. Tycker du om att bli smekt på ollonet?

- ☐ Ja, mycket
- ☐ Ja, delvis
- ☐ Nej
- ☐ Vet inte

Uppföljning rörande sexuell lust/libido

Följande frågor handlar om sexuell lust och libido. De är inte beroende av att man ska ha debuterat sexuellt ännu.

52. Har du debuterat sexuellt?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

53. Är du intresserad av sex?

1=Nej, inte alls 10= Ja, mycket

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

54. Kan du få erektion (stånd?)

- ☐ Ja, ibland
- ☐ Ja, utan problem
- ☐ Nej
- ☐ Vet inte

55. Om ja, är du nöjd med din erektion?

_____

_____

56. Har du blivit sexuellt upphetsad den senaste månaden?

- ☐ Ja, flera ggr varje dag
- ☐ Ja, varje dag
- ☐ Ja, 7-15 gånger
- ☐ Ja, 4-6 gånger
- ☐ Ja, 1-3 gånger den senaste
- ☐ månaden
- ☐ Nej, ingen gång
- ☐ Vet inte

57. Kan du få orgasm vid smekningar?
Med smekningar menas både av dig själv och partner.

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

58. Har du ejakulat (utlösning) i samband med orgasm?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

59. Är du intresserad av kroppslig kontakt med din partner?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Med kroppslig kontakt menas här beröring i form av pussar, kramar, kyssar, smekningar, sexuellt umgänge.

60. Om du inte tycker om att ha kroppslig kontakt med din partner, har du någon uppfattning om varför?

_____

61. Hur ofta har du tänkt på sex den senaste månaden?

- ☐ Flera ggr per dag
- ☐ Dagligen
- ☐ 2-6 ggr per vecka
- ☐ 4-7 ggr per månad
- ☐ 1-3 gr per månad
- ☐ < 1 gång/månad

62. Hur många gånger har du tillfredställt dig själv sexuellt den senaste månaden?

- ☐ Varje dag
- ☐ 4–6 gr senaste månaden
- ☐ 1–3 gr senaste månaden
- ☐ Ingen gång
- ☐ Vet inte

63. Har hypospadin påverkat ditt kärleksliv negativt?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om hypospadin har påverkat ditt kärleksliv, kan du beskriva hur?

_____

_____

Om du ej har debuterat sexuellt kan du gå direkt till fråga 81!

64. Kan du genomföra ett samlag med penetration?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

65. Hur gammal var du när du hade penetrerande sex första gången? _____

66. Upplever du smärta vid samlag?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

67. Kan du få orgasm vid samlag?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Om du inte kan få orgasm vid samlag, har du någon uppfattning om varför?

_____

_____

68. Har du/har du haft impotensbesvär?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

69. Har du fått någon behandling mot impotens (ex Viagra, Bondil, Uprima, Caverject el annat)?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

70. Om du har haft impotensbesvär: Under vilken/vilka perioder? Hur ofta?

71. Om du har fått behandling, vilken, vilken dos? Fungerade behandlingen?

72. Är du nöjd med ditt sexualliv?

- ☐ Ja, mycket
- ☐ Ja, ganska
- ☐ Nej, inte speciellt
- ☐ Nej, inte alls

73. Har du regelbundet sexuellt samliv?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

74. Ungefär med hur många har du haft sexuella relationer?

- ☐ 0-1
- ☐ 2-4
- ☐ 5-7
- ☐ 8-10
- ☐ 11-15
- ☐ 16-20
- ☐ >20
- ☐ Vet inte

75. Ungefär hur ofta har du sex?

- ☐ Aldrig
- ☐ 1 g/dag
- ☐ 3-5 ggr/vecka
- ☐ 1-2 ggr/vecka
- ☐ 2-4 ggr/månad
- ☐ 1g /månad
- ☐ < 1/månad
- ☐ Vet inte

76. Hur ofta skulle du vilja ha samlag varje månad?

- ☐ Aldrig
- ☐ 1 g/dag
- ☐ 3-5 ggr/vecka
- ☐ 1-2 ggr/vecka
- ☐ 2-4 ggr/månad
- ☐ 1g /månad
- ☐ < 1/månad
- ☐ Vet inte

77. Har du en partner för närvarande?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

78. Vem tar oftast initiativ till sex?

- ☐ Du
- ☐ Din partner
- ☐ Båda lika ofta
- ☐ Har ingen partner

☐ Vet inte

79. Kan du och din partner prata om ert sexuella samliv?

☐ Ja
☐ Nej
☐ Vet inte

80. Hur skulle du beskriva din förmåga att njuta av sex?

☐ Alltid tillfredsställande
☐ Ibland tillfredställande
☐ Sällan tillfredställande
☐ Aldrig tillfredställande
☐ Vet inte

81. Sexualitet
Ringa in det alternativ som stämmer bäst in på dig.

The questions are part of the questionnaire by Hines concerning sexuality, not published because of copywrite reasons.

Övriga frågor

82. Har du regelbunden kontakt med läkare nu?

☐ Ja
☐ Nej
☐ Vet inte

83. Skulle du vilja ha mer kontroller hos läkare på grund av detta?

☐ Ja
☐ Nej
☐ Vet inte

84. Har du behov av samtalskontakt (psykolog/sexolog)?

☐ Ja
☐ Nej
☐ Vet inte

85. Har du någonsin haft behov av samtalskontakt?

☐ Ja
☐ Nej
☐ Vet inte

86. Hur tycker du att sjukvården ska hantera pojkar/män med hypospadi vad det gäller antal läkarkontroller?

☐ Bara efter operation
☐ <1 g/år
☐ 1-4 ggr/år
☐ >4 ggr/år
☐ Vet inte

87. Hur tycker du att sjukvården ska hantera pojkar/män med hypospadi vad det gäller tidpunkt (ålder) för operation?

☐ <1 års ålder
☐ 1-3 års ålder

- ☐ 4-7 års ålder
- ☐ 8-11 års ålder
- ☐ 12-15 års ålder
- ☐ 16-18 års ålder
- ☐ > 18 års ålder
- ☐ Vet inte

Nu kommer ett antal grupper av frågor som berör mer psykologiska områden. Det är ibland många frågor i varje grupp av frågor, men ägna inte för mycket tid åt varje fråga, utan svara snabbt utan att tänka för mycket.

En del frågor som handlar om t.ex könsidentitet kan tyckas onödiga i denna grupp av patienter, men det är för att ni också fungerar som kontrollgrupp till andra grupper av patienter med mer allvarliga åkommor.

88. Besvara frågorna nedan genom att skatta dig själv med hjälp av skalan till höger. För varje fråga, sätt ett kryss i den ruta som bäst beskriver hur du har känt och betett dig de senaste 6 månaderna.

ASRS Questionnaire, concenring symptoms of ADHD, not published because of copywrite reasons.

89. Nedan följer ett antal påståenden. Kryssa i den ruta som du själv tycker stämmer bäst in på dig för varje påstående.

BES Questionnaire concerning body esteem, not published because of copywrite reasons.

<u>Sinnestillstånd</u>

Avsikten med nedanstående frågor är att ge en detaljerad bild av ditt nuvarande sinnestillstånd. Vi vill alltså att du skall försöka gradera hur du mått den senaste tiden. Formuläret innehåller en rad olika påståenden om hur man kan må i olika avseenden. Påståenden uttrycker olika grader av obehag, från frånvaro av obehag till maximalt uttalat obehag.

Markera den siffra som du tycker stämmer med hur du mått de senaste tre dagarna. Tänk inte alltför länge, utan försök arbeta snabbt.

CPRS-S-A Questionnaire concerning depression, anxiety and compulsive disorder syndromes, not published because of copywrite reasons.

109. Har du blivit mobbad någon gång?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Kommentar:_____
_____

110. Har du någon gång mobbat andra?

- ☐ Ja
- ☐ Nej
- ☐ Vet inte

Kommentar:_____
_____

Könsidentitet och könsroller

Questions part of the questionnaire by Hines concerning gender identity and gender role behavior, not published because of copywrite reasons.

Denna fråga handlar om livskvalitet. Kryssa i det alternativ som passar Dig bäst. Endast ett kryss per fråga.

PGWB Questionnaire, concerning QoL, not published because of copywrite reasons.

234. Olika sätt att relatera till andra människor

Instruktioner:
Nedan beskriver vi fyra olika sätt att uppleva relationer till andra människor. Ringa in den siffra Du anser passar in på just Dig, när Du tänker på hur Du fungerar i relationer med andra.

Relationship questionnaire (RQ), concerning how people attach to other people, not published because of copywrite reasons.

Har du ytterligare synpunkter som du vill förmedla?

_____
_____
_____
_____

Hur tycker du det har varit att delta i denna undersökning?

Kryssa det värde som motsvarar ditt svar.
0= Mycket jobbigt 3=Lite jobbigt 5=Helt ok 7=Inga problem 10=Trevligt

[---I---I---I---I---I---I---I---I---I---]
1 2 3 4 5 6 7 8 9 10

Skriv gärna ytterligare kring hur det varit att deltaga i denna undersökning här!

_____
_____
_____
_____
_____
_____

Tack för ditt deltagande!
Posta din enkät i det bifogade frankerade kuvertet!

Appendix B. The Case report form.

CRF-uro us

Kod nr:_____

Hypospadi

Långtidsuppföljning av män opererade för hypospadi

Allmänt: Intro ang. hypospadi, vad undersökningen består av etc.

Kommentarer_____

För definitioner- se manualen!

Operation:

☐ Signerat för kopia journal
☐ Op-journaler tillgängliga

Operationsår:_____

Operationstyp:☐ Glansop ☐Mathieu ☐Dennis-Brown ☐Annat?

Opererad var:_____
Antal operationer:_____
Op plissering ☐ ja ☐nej

Flödeskurva:

☐ Flödeskurva utfört

Maxflöde:_____ml/s Flödestid:_____sek
Totalvolym:_____ml Form: ☐klocka ☐platå ☐fraktionerad ☐ Annat

Andra medfödda missbildningar:

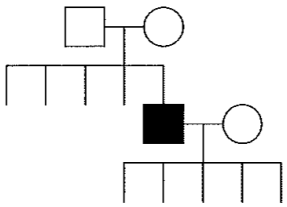
Vilken annan missbildning?_____

Opererad för denna missbildning?_____

☐ Retentio testis
☐ Njurar/urinvägar
☐ Händer/fötter
☐ Hjärta
☐ Annat

☐ Prematur, född i vecka:_____
Födelsevikt:_____g

Pedigree (för hypospadi +övr missb.):



CRF-uro us

Kod nr:_____

Mått: *(us i liggande, se manualen)*

Penis (hela) *Mått:*
- ☐ längd ____ mm
- ☐ bredd ____ mm
- ☐ omkrets ____ mm
- ☐ chordee ☐ 0-10⁰ ☐ 10-30⁰ ☐ 30-60⁰ ☐ 60-90⁰ ☐ endast glanstipp
- ☐ längd vid erektion _____ (halv/hel cm) (mätt eller frågat)

Glans *Mått:*
- ☐ längd ____ mm
- ☐ bredd ____ mm
- ☐ omkrets ____ mm
- ☐ erektion i glans ☐ ja ☐ nej

Penis sedd från sidan	Penis sedd framifrån

Meatus *Kryssa i platsen för meatus*
Utseende
- ☐ u.a
- ☐ atypisk (rita)

Avstånd
- ☐ corona-meatus: _____cm
- ☐ meatus-penis bas:____cm

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

Fistel ☐ ja ☐ nej
*Läge:*_____

Preputium
- ☐ circumciderad
- ☐ ej cirkumciderad
  - ▷ ☐ kluvet
  - ▷ ☐ cirkulärt

Tecken till BXO
☐ ja ☐ nej

Skrotum (us i stående)
- ☐ symmetrisk, normal
- ☐ testiklar i skrotum bilat

Läge testikel hö sida:_____
Volym höger:_____ml
Läge testikel vä sida:_____
Volym vänster:____ml
- ☐ bifid skrotum

Tecken till varicocele
☐ ja ☐ nej

Behåring (övre begränsning)
- ☐ rak
- ☐ upp i medellinjen
- ☐ rakad

Transposition
- ☐ nej
- ☐ mild partiell
- ☐ svår partiell
- ☐ total

Sensibilitet glans
(testad med öronpinne)
(+ motsvarar lårets insida)

Grad, kryssa
- ☐ +++
- ☐ ++
- ☐ +
- ☐ 0

Ev.kommentarer: ska studeras
hur!_____vibration_____
_____temperatur_____
_____monofilament_____
En-två-punktsdiskrimination_____

Ärrighet
- ☐ Nej
- ☐ Ja (rita på skissen)

CRF-uro us Kod nr:_____

Foto:

☐ Foto taget; I stående framifrån 2D:_____
☐ Foto taget; dorsalflekterad 4D:_____
☐ Foto taget; från sidan, upprest Kvot 2D/4D:_____

Provtagningar:

☐ EDTA (DNA-diagnostik)
☐ Heparinrör (karyotyp) Resultat av kromosomanalys: ☐46, xy ☐Annan:_____
☐ Testosteron Resultat:_____
☐ DHT Resultat:_____
☐ LH/FSH Resultat:_____
☐ Urinprov (steroidprofil) Resultat:_____

Undersökning utförd av: _____datum_____

CRF-uro us Kod nr:_____

MANUAL för undersökning vid långtidsundersökning av hypospadi
Definition av begrepp

"Signerat för kopia journal" d.v.s. att patienten godkänt rekvisition av journalen
Op-journaler tillgängliga, bör helst rekvireras innan mottagningsbesöket.

Operationstyper

Flödeskurva: klocka, platå, fraktionerad- kryssa i rätt alternativ samt sätt fast flödeskurvan på CRF-formuläret.

Andra missbildningar hos patienten och i familjen i övrigt

Pedigree:
Fyrkant = man/pojke Ofylld= frisk och ifylld = sjuk
Cirkel = kvinna/flicka
Ifylles med avseende på både hypospai samt ev andra missbildningar i släkten.

Penis undersöks med patienten liggande på britsen
Längden mäts mot höger pekfinger med fingerspetsen in dikt an mot symfysen och i sträckt läge av penis och längden stämmes av mot fingret som jämförs med en linjal liggande på bordet. Mät gärna undersökarens finger innan!
Bredd och omkrets mäts mitt på skaftet; mät med ett snöre och kontrollera måttet mot linjalen.
Kurvering anges höftat i intervallet 0-10, 10-30, 30-60, 60-90 grader. Specialfall; tipp av själva glans med rakt penisskaft.
Mått penislängd vid erektion efterfrågas i enkäten. Mätes om möjligt vid undersökningen.
Mått på glans mäts med snöre och jämförs mot linjalen på bordet.
Bredd mäts på bredaste stället.
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, mätes 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, ej opererat d.v.s. kluvet eller ihopsytt med en plastik d.v.s. cirkulärt.

"Tecken till BXO" d.v.s. 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.

Beskriv **behåringens** övre begränsning som rak eller upp i medellinjen, ange eventuell annan patologi.

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.

Sensibilitet på glans testas med en bomullstops där "+" innebär samma känsel som vid beröring med topsen på lårets insida. "+++" anger en mycket bra känsel. Innan de svåraste patienterna ska undersökas ska vi ta reda på om annan metod kan användas också, till exempel vibration, temperatur, en och tvåpunktsdiskrimination med gem eller monofilament (dvs mäter tryck noggrant och används vid undersökning av känsel på fötterna hos diabetiker).

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 tejpbild 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!

Undersökningen avslutas med blodprovstagning. Ungefärlig kostnad inom parentes.

1. EDTA-rör, ta 3-10 ml, för att isolera DNA (görs som forskning huvudman And)
2. Heparinrör, 1-3 ml vid "svår hypospadi" för att göra en karyotyp
3. Rör utan tillsats för mäta testosteron, LH och FSH
4. Rör utan tillsats för att bestämma DHT

Urinprov skickas för undersökning av steroidprofil.

Svaren på us 2-4 skrivs in eller bifogas. Formuläret.

Transport av blodprover:
EDTA-röret skickas till "Agneta Nordenskjöld, CMM:02, Karolinska universitetssjukhuset, 17176 Stockholm" för isolering av DNA och lagring i biobank tills mutationsanalys sker enligt forskningsplanen. Detta prov kan även användas för att göra sk QF-PCR. Denna analys ersätter en karyotyp eftersom det ger svar på eventuella könskromosomaberationer. Frankerade svarskuvert finns för detta. Kan rekvireras hos Agneta.

Heparinröret skickas till respektive avdelning för klinisk genetik. Karyotypen skrives in i CRF-formuläret.

Övriga rör skickas till respektive labb för analys. Resultaten skrivs in i CRF-formuläret.