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92

# Hypospadias Surgery

## Outcome and Complications

HANS WINBERG

DEPARTMENT OF CLINICAL SCIENCES | LUND UNIVERSITY





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## Hypospadias Surgery



# Hypospadias Surgery

## Outcome and Complications

Hans Winberg, MD



**LUND**  
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DOCTORAL DISSERTATION

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To be defended at Segerfalksalen. May 9<sup>th</sup>, 2020, 09:00

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| <b>Abstract</b><br>The aim was to evaluate complications following hypospadias repair and correlate them to pre- and postoperative symptoms, degree of hypospadias and surgical procedures.<br><b>Methods</b><br>The fundament was a cohort from a prospectively collected register including boys who underwent primary repair of hypospadias by the Mathieu procedure or tubularised incised plate (TIP) repair for grade 1–2 hypospadias. Controls were used for analysis of postoperative urinary tract infections. A meta-analysis was performed comparing the two surgical procedures regarding major complications: fistulas and strictures. Urinary flow measurements were conducted to evaluate whether signs of obstruction might precede any development of fistula.<br><b>Results</b><br>There were no significant differences between the Mathieu procedure or TIP repair regarding frequency of major surgical complications (Clavien-Dindo IIIb), whether they were preoperative symptoms or the degree of hypospadias. The presence of postoperative positive urinary cultures differed between boys who had hypospadias surgery (7.5%), and boys operated on for inguinal hernia (1.5%) ( $p < 0.01$ ). A higher incidence of urinary tract infections was noted in boys who had concomitant congenital malformations in addition to hypospadias (34% [10 of 29] versus 0.5%) ( $p < 0.01$ ).<br>In our material the Mathieu procedure was followed by a higher frequency of reoperations compared to TIP repair ( $p < 0.01$ ) but in the meta-analysis the Mathieu procedure was favoured regarding urethral stricture. Urinary flow measurement could not single out those boys at risk of developing urethral fistulas.<br><b>Conclusions</b><br>The overall risk of complications after hypospadias repair does not correlate to the degree of hypospadias or preoperative symptoms. Therefore, surgery in boys with hypospadias without symptoms could be questionable. Boys with hypospadias are likely to be affected by urinary infections.<br>The postoperative complication rate in our local cohort decreased after transition from the Mathieu procedure to TIP repair but, according to the meta-analysis, strictures were less common after the Mathieu procedure compared to TIP repair.<br>The results reject the hypothesis that urinary flowmetry enables an early detection of the postoperative complication of fistula after hypospadias surgery. |                         |  |  |
| <b>Key words</b><br>Hypospadias repair; Boys; Preoperative Symptoms; Age; Meatal Location; Outcome; Complications; Urinary tract infections; Reconstruction; Urinary flow measurements; Fistula; Meta-analyses; Mathieu (PBF); Tubularised incised plate repairs (TIP); Urethrocutaneous fistula; Urethral stricture.  |                         |  |  |
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# Hypospadias Surgery

## Outcome and Complications

Hans Winberg, MD



**LUND**  
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Doctoral thesis

2020



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*To all boys with hypospadias who require surgery,  
and those who do not*

# Table of Contents

|   |           |
|---|-----------|
| Thesis in brief.....  | 10        |
| Papers included in this thesis .....                        | 11        |
| Abstract .....  | 12        |
| <b>Introduction.....</b>                                    | <b>15</b> |
| Male sex development .....                                  | 15        |
| Hypospadias characteristics.....                            | 17        |
| The fundamentals of the thesis, questions and problems..... | 19        |
| <b>Aim of project .....</b>                                 | <b>23</b> |
| <b>Settings and patients .....</b>                          | <b>25</b> |
| Papers I, II, III and V .....                               | 25        |
| <b>Methods.....</b>   | <b>27</b> |
| Papers I, II, III and V .....                               | 27        |
| Study design .....  | 27        |
| The surgical methods.....                                   | 27        |
| Perioperative regimen .....                                 | 31        |
| Clinical follow-up and outcome.....                         | 32        |
| Paper IV: Meta-analysis .....                               | 34        |
| Ethical considerations.....                                 | 36        |
| Statistical analysis .....                                  | 36        |
| <b>Results .....</b>  | <b>39</b> |
| Paper I.....  | 39        |
| Paper II.....   | 41        |
| Paper III .....   | 42        |
| Paper IV .....  | 43        |
| Paper V.....  | 47        |

|  |    |
|--|----|
| <b>Discussion</b> .....  | 51 |
| Complications and correlation with symptom, degree and method of operation (Paper I).....              | 51 |
| Risk of UTI in boys with hypospadias (Paper II).....   | 53 |
| Does a change of surgical method affect the complication rate in hypospadias surgery? (Paper III)..... | 55 |
| Meta-analysis comparing the outcome of two methods of distal hypospadias repair (Paper IV) .....       | 56 |
| Urinary flow measurements and the prediction of fistulas (Paper V) .....                               | 58 |
| Strength and limitations and risk of bias in Papers I–V .....  | 59 |
| <b>Conclusion</b> .....  | 61 |
| <b>Future aspects</b> .....  | 63 |
| <b>Populärvetenskaplig sammanfattning</b> .....  | 65 |
| <b>Acknowledgements</b> .....  | 67 |
| <b>References</b> .....  | 69 |

# Thesis in brief

|                | The aim of the study   | Methods  | Results  | Conclusions  |
|----------------|--|--|--|--|
| <b>Paper 1</b> | To assess the rate of complications following hypospadias repair and to correlate them with the preoperative symptoms, degree of hypospadias and method of operation. This study was conducted to address the question of whether all boys with any degree of hypospadias should undergo reconstruction. | A prospective cohort study included 76 boys who underwent surgery for primary repair of hypospadias. The main outcome measurements were the frequency of postoperative complications and their correlation with the degree of hypospadias, the preoperative symptoms and the operative intervention performed.           | Preoperatively, 43 of the boys had symptoms that prompted the operation, including stenosis (38), a curvature (10) or both (5). There were complications requiring reoperations including fistulas or ruptures in 26 (34%) boys. There were no significant differences in the rates of complications with surgery, fistulas ( $p = 0.4775$ ), ruptures ( $p = 0.2417$ ) or other complications ( $p = 0.5165$ ) between the groups with or without preoperative symptoms, those with different degrees of hypospadias or those who underwent different operative methods for repair.   | The complication rate did not correlate with the degree of hypospadias nor the preoperative symptoms. Surgery is questionable in boys with hypospadias without symptoms.         |
| <b>Paper 2</b> | To evaluate the frequency of urinary tract infections (UTI) in boys with hypospadias pre- and postoperatively in order to determine whether antibiotic prophylaxis for UTI is warranted in reconstructive surgery for hypospadias.   | A study of 174 boys undergoing reconstructions for hypospadias and a control group comprised of 204 boys operated on for an inguinal hernia. The main outcome measure was the documented finding of a UTI verified by a positive bacteria culture.   | The results revealed a significant difference in the findings of a positive urinary culture between the boys undergoing hypospadias surgery, 7.5%, and those operated on for an inguinal hernia, 1.5% ( $p = 0.0044$ ). The difference between the groups was not significant in the pre- and peri-operative periods. A higher incidence of infections was noted in boys who had other congenital malformations in addition to hypospadias ( $p = 0.02$ ).   | Boys with hypospadias are more likely to incur a UTI.  |
| <b>Paper 3</b> | To analyse if a change of surgical method affects the complication rate in hypospadias surgery.  | An observational study where the Mathieu procedure had been replaced by the TIP repair as the most favoured method of grade 1–2 hypospadias repair. All operated boys were registered prospectively during two 3-year-periods with equal number of patients. The end point was any complication requiring a reoperation. | In the first period 69 boys were operated on, of whom 50 underwent the Mathieu procedure and 19 TIP repair. 35 (51%) boys required a reoperation. In the second period 73 boys were operated on of whom 19 underwent the Mathieu procedure and 54 TIP repair. 15 (21%) required a reoperation, $p < 0.01$ .  | The surgical method seems to matter. Advantage TIP repair.   |
| <b>Paper 4</b> | To compare the two major complications, namely postoperative urethrocutaneous fistula and urethral stricture, between the Mathieu and tubularised incised plate (TIP) repair methods for distal hypospadias.   | In a meta-analysis, electronic databases were searched for comparative studies on the two techniques. The Oxford Centre for Evidence-based Medicine Levels of Evidence (CEBM) was used to evaluate the included studies. The main outcome measure was the frequency of postoperative fistula and urethral stricture.     | Included were 17 studies, comprising 1572 patients. The frequency of urethrocutaneous fistula was the same, 13%, for both the Mathieu and TIP methods (odds ratio (OR) 1.1, 95% confidence intervals (CI) 0.6–1.9, $p = 0.73$ ). Urethral stricture was less frequent after the Mathieu (2%) procedure than after TIP (5%) repair (OR 0.5, 95% CI 0.3–0.8, $p < 0.01$ ), even after the subgroup analysis of eight randomised controlled trials (RCTs) was included. Overall, the quality of the included studies was determined to be satisfactory. The levels of evidence on which this review was based ranged from 1b to 2b using the CEBM Levels of Evidence. | Compared with TIP repair, the Mathieu procedure for hypospadias had a significantly lower risk of urethral stricture; however, the risk of urethrocutaneous fistula was similar. |
| <b>Paper 5</b> | To test the hypothesis if it is possible to anticipate and prevent the development of fistulas after hypospadias repair by assessing urinary flow measurements.  | An observational and interventional study where urinary flow measurements were conducted 4–6 weeks postoperatively.  | There was no difference detected in the urinary flow measurements of the boys developing the postoperative complication of urethral fistula and those who were not affected by this complication.  | The results do not support the hypothesis that it is possible to detect the postoperative complication of a fistula after hypospadias surgery.                                   |

## Papers included in this thesis

This thesis is based on the following original papers, which are referred to in the text by their Roman numerals:

- I. Winberg H, Westbacke G, Ekmark AN, Anderberg M and Arnbjörnsson E. The Complication Rate after Hypospadias Repair and Correlated Preoperative Symptoms. *Open Journal of Urology*. 2014;4:155-162. <http://dx.doi.org/10.4236/oju.2014.412027>
- II. Winberg H, Jinhage M, Träff H, Salö M, Westbacke G, Nozohoor AE, Anderberg M, Arnbjörnsson E. Urinary Tract Infection in Boys with Hypospadias. *MOJ Surg*. 2016;3(3):55-59. DOI: 10.15406/mojs.2016.03.00045
- III. Winberg H, Anderberg M, Arnbjörnsson E. Tubularized Incised Plate (TIP) Repair Improves Outcome of Hypospadias Repair. *J Surgery*. 2016;4(2): 4. <https://doi.org/10.13188/2332-4139.1000033>
- IV. Winberg H, Arnbjörnsson E, Anderberg M, Stenström P. Postoperative outcomes in distal hypospadias: a meta-analysis of the Mathieu and tubularized incised plate repair methods for development of urethrocutaneous fistula and urethral stricture. *Pediatr Surg Int*. 2019;35(11):1301-1308 <https://doi.org/10.1007/s00383-019-04523-z>
- V. Winberg H, Anderberg M, Arnbjörnsson E, Stenström P. Urinary flow measurement in hypospadias. Accepted for publication in *Journal of Pediatric Urology*.

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**Paper I:** Oral presentation at the 4th World Congress of Pediatric Surgery (WOFAPS) October 2013, Berlin, Germany. (A-587-0025-00540)

**Paper II:** Oral presentation 5th World Congress of Pediatric Surgery (WOFAPS) October 2016, Washington, USA.

**Papers III** presentation at the Swedish Surgical Week in 2016

**Paper IV** presentation at the Swedish Surgical Week in 2019

# Abstract

## *Aim*

To evaluate complications following hypospadias repair and correlate them to pre- and postoperative symptoms, degree of hypospadias and surgical procedures.

## *Methods*

The fundament was a cohort from a prospectively collected register including boys who underwent primary repair of hypospadias by the Mathieu procedure or tubularised incised plate (TIP) repair for 1–2-degree hypospadias. Controls were used for analysis of postoperative urinary tract infections. A meta-analysis was performed comparing the two surgical procedures regarding major complications, i.e. fistulas and strictures. Urinary flow measurements were conducted to evaluate if signs of obstruction might precede any development of fistula.

## *Results*

There were no significant differences between the Mathieu procedure and TIP repair regarding frequency of major surgical complications, prompting a procedure under general anaesthesia, Clavien-Dindo IIIb, no matter what the preoperative symptoms or the degree of hypospadias. The presence of postoperative positive urinary cultures differed between boys who had hypospadias surgery (7.5%), and boys operated on for inguinal hernia (1.5%) ( $p < 0.01$ ). A higher incidence of urinary tract infections was noted in boys who had concomitant congenital malformations in addition to hypospadias (34% [10 of 29] versus 0.5%) ( $p < 0.01$ ).

In our study the Mathieu procedure was followed by a higher frequency of reoperations compared to TIP repair ( $p < 0.01$ ), but in the meta-analysis, the Mathieu procedure was favoured regarding urethral stricture. Urinary flow measurement could not single out boys at risk of developing urethral fistulas.

## *Conclusions*

The overall risk of complications after hypospadias repair does not correlate to the degree of hypospadias or preoperative symptoms. Therefore, surgery in boys with hypospadias without symptoms might be questionable.

Boys with hypospadias are likely to be affected by urinary infections.

The postoperative complication rate in our local cohort decreased after transition from the Mathieu procedure to TIP repair, but according to the meta-analysis, strictures were less common after the Mathieu procedure compared to TIP repair.

The results reject the hypothesis that urinary flowmetry enables an early detection of the postoperative complication of fistula after hypospadias surgery.



## **Keywords**

Hypospadias repair; Boys; Preoperative Symptoms; Age; Meatal Location; Outcome; Complications; Urinary tract infections; Reconstruction; Urinary flow measurements; Fistula; Meta-analyses; Mathieu (PBF); Tubularised incised plate repairs (TIP); Urethrocutaneous fistula; Urethral stricture

## **Abbreviations**

AMH: anti-Müllerian hormone

CEBM: (Oxford) Centre of Evidence Based Medicine

DHT: dihydrotestosterone

HOSE: hypospadias objective scoring evaluation

LUTS: lower urinary tract symptoms

PBF: perimeatal based flap, i.e. the Mathieu repair

PPPS: paediatric penile perception score

PVR: post-void residual volume

RCT: randomised controlled study

SRY gene: sex-determining region of the Y chromosome

TIP: tubularized incised plate repair

UTI: urinary tract infection

## **Definitions**

Q max (ml/s): maximum flow rate

Voided volume (ml): volume of urine delivered during the measurement

Voiding time (s): duration of the voiding procedure

Time to Q max (s): duration of time from the beginning of voiding to maximal urinary flow

Q ave (ml/s): average flow rate

PVR (ml): post-void residual urinary bladder volumes



# Introduction

Hypospadias is a common malformation affecting almost 8 in 1000 boys in Sweden (1). Hypospadias means that the opening of the urethra, the meatus, fails to reach the tip of the glans penis during development and therefore becomes located somewhere along the ventral side of the penis. The malformation is a midline anomaly and can be of varying severity, usually divided into degrees, according to where the meatus is situated. The more proximal, the more complex the anomaly, and more complex cases may also present with curvature of the penis. The proximal hypospadias account for up to 30% of all cases of hypospadias (2).

In the mildest forms, the only sign of a midline anomaly might be the cleaved foreskin exposing a well-formed meatus in or near the correct location. In these boys, physical symptoms are rare. In distal hypospadias the meatus is sometimes rudimentary which influences urinary flow by obstruction. The natural course of untreated hypospadias is not well studied because the great majority of boys are treated surgically. The result of a conservative approach, when it comes to function and appearance, could only be evaluated after puberty, but it could be expected that a pronounced curvature of the penis might interfere with penetrating intercourse.

While the treatment is surgical there is as yet a lack of consensus of opinion on the ideal treatment of hypospadias, and complications resulting from surgery are common.

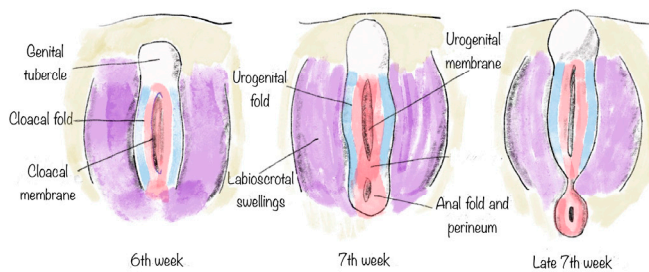
## Male sex development

At fertilisation, the chromosomal sex is determined by the fusion of the ovum containing an X chromosome and the sperm, carrying either an X or Y chromosome. After an initial quiescent phase of about 6 weeks, the gonadal tissues begin to differentiate into testes or ovaries depending on which sex chromosomes are present. Either type of gonad is then responsible for the development of the phenotypic sex, male or female, defined by the internal and external genitalia and secondary sex characteristics (3).

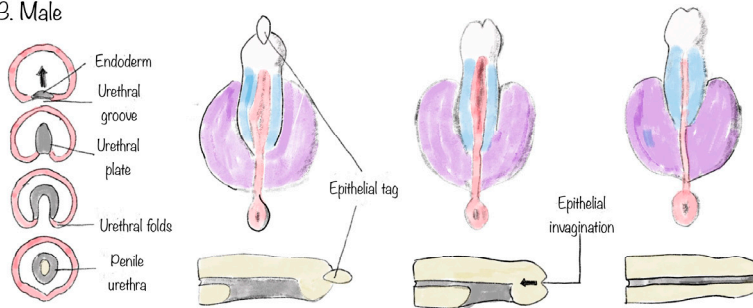
### *Differentiation of male internal genitalia*

In the presence of a Y chromosome and its SRY gene (sex-determining region of the Y chromosome), the gonadal ridges develop towards testicular tissue. The subsequent hormonal action will lead to male phenotypic sex development. The gonad is driven to Sertoli cell differentiation and their subsequent release of anti-Müllerian hormone (AMH) will lead to regression of female primordial internal genitalia. The Sertoli cells also, in conjunction with foetal and placental hormones, secrete factors that stimulate the development of Leydig cells with concomitant production of testosterone. This will induce the differentiation of male internal genitalia into the seminal vesicles, vas deferens and epididymis.

#### A. Indifferent stage



#### B. Male



JW 20

**Figure 1.** Differentiation of male external genitalia.

### *Differentiation of male external genitalia*

In the primordial external genitalia testosterone is converted locally to the more potent dihydrotestosterone (DHT) which is required for the virilisation process initiated from foetal week 9. DHT stimulates the androgen receptor to promote fusion of the labioscrotal folds with a lengthening of the anogenital distance and elongation of the genital tubercle into a phallus (3–5). With the lengthening of the genital tubercle the

epithelium-covered urethral groove develops ventrally and is referred to as the urethral plate. The urethral plate fuses medially like a zipper in a proximal to distal direction. It forms a tube communicating proximally with the urogenital sinus and the developing prostatic and membranous urethra, and distally reaching the glans penis. The most distal glanular part is proposed to arise from ectodermal ingrowth from the glans, fusing with the penile urethra. By fusion of the outer genital folds, the corpus spongiosum and the corporeal bodies are shaped in the proximal to distal direction. Finally, the foreskin is closed over the glans at the end of the 20th week of gestation (5–7).

## Hypospadias characteristics

In some cases, the differentiation into the male phenotypic sex does not follow the expected course and results in atypical external genitalia. Hypospadias is mainly characterised by a meatus short of the tip somewhere on the ventral side of the penis, a ventral curvature and a cleaved, hood-resembling foreskin, assembled dorsally. There might be a meatal stenosis which is important to recognise.

With the meatus in an abnormal position, perhaps even narrow, the boy might have problems with the direction of the urinary stream and display obstructive signs. Older boys and men can suffer from a ventral curvature with painful erections and difficulties in performing sexual intercourse.

The position of the meatus depends on when the zipper-like tubularisation of the urethra fails during foetal development. The lesser anomaly results in a slightly misplaced meatus and a cleaved foreskin. If the anomaly occurs early, it can affect the fusion of the whole urethra, as well as the genital folds, resulting in a near perineum meatus and bifid scrotum or even ambiguous genitalia (8).

It is important to understand that the obvious malformation could be described as just the tip of the iceberg, and that the malformation also includes surrounding tissues. The surrounding anomaly can interfere with healing and it may have implications for surgical strategy.

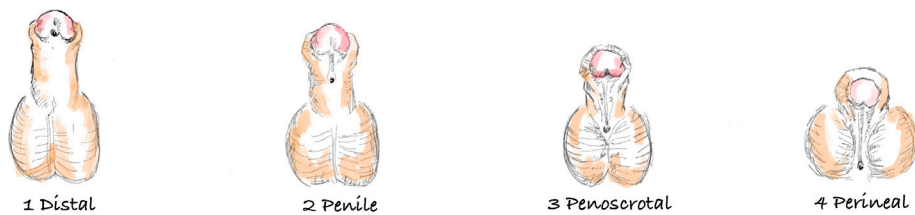
A ventral curvature is present in distal hypospadias; it is mainly the result of deficient skin length and periurethral growth (8).

On the other hand, in proximal hypospadias, the corpus spongiosum, which is supposed to enclose the penile urethra to the tip of the penis, is divided and hypoplastic. As a result of the lack of androgen action this, and other hypoplastic and even apoptotic ventral tissues such as the urethral plate, contribute to the curvature (8).

Usually, the hypospadias is obvious because the foreskin fails to cover the glans, but in rare cases intact foreskin covers the misplaced meatus and therefore the malformation is revealed during circumcision or after puberty.

The spectrum of hypospadias also features penoscrotal transposition, penile torsion, webbed or concealed penis, glans tilt and the so-called cryptohypospadias with a curvature but with the meatus in the correct position.

The great diverseness of the phenotype is important to describe correctly, to enable research and to plan surgery. Presently, the most common classification system is based on the location of the meatus, taking into consideration any curvature that after a straightening procedure enhances the degree of the hypospadias (8,9).



**Figure 2.** Phenotypes of hypospadias.

### *Definitions of hypospadias*

The different types of hypospadias have been classified according to the preoperative position of the urethral meatus as follows (10):

- Degree 1: glanular hypospadias with the meatus located on the glans or in the sulcus coronaries;
- Degree 2: distal hypospadias with the meatus located subcoronally or on the mid-shaft of the penis;
- Degree 3: with the meatus located penoscrotally or scrotally.
- Degree 4: with the meatus located perineally

In cases where a curvature was present, the classification of the hypospadias was made after the straightening procedure.

## The fundamentals of the thesis, questions and problems

Globally, hypospadias is one of the most common congenital anomalies (11). The reconstruction for this condition is a delicate procedure and the ideal method of repair for hypospadias is still under debate. More than 300 different operations have been described in the literature for the treatment of this condition (11). The considerable number of different operative interventions might reflect the frustration of surgeons facing the high rate of complications — reoperation rates can exceed 50% after primary repair (11) — that result from hypospadias repair. Also, in Sweden we identified a great diversity of methods being used at different centres which was acknowledged during the formation of a national hypospadias guidelines group. Hence the ambition in Sweden has been to reduce the number of methods to a few alternatives whereby a glanuloplasty or conservative treatment is recommended for the first-degree distal hypospadias, TIP repair for second degree and a few different variants of two-stage procedures for the third to fourth degree proximal hypospadias (12).

Uniform definitions have also been missing as to how to assess complications and outcome. Functional outcome is usually assessed with uroflowmetry and measurements of residual volumes after micturition. Patients who have been operated on for hypospadias run a double risk of lower urinary tract symptoms (LUTS) compared to controls (13).

With regard to the cosmetic result, there are several questionnaires available with their own pros and cons, such as the (Pediatric) Penile Perception Score (PPPS) and the Hypospadias Objective Scoring System (HOSE). Yet there is no validated questionnaire for the evaluation of psychosexual function (2,14,15). However, 70% of responding patients are reported to experience satisfaction with the cosmetic outcome after hypospadias repair (50% in the proximal group) and 80% report to have satisfactory sexual function (13). To gain deeper understanding and knowledge about patients' needs for long-term follow-up and treatment, reports from different centres, and comparisons between them, are important. True and transparent presentation of standardised data is mandatory to increase the quality of research with the intention to refine hypospadias repair as the majority of research is based on observational studies (2).

The goal of surgery is normalisation of function and cosmetic appearance. For function, indications for surgical repair include diverted spraying of the urinary stream, inability to void in a standing position, a pronounced curvature of the penis assumed to interfere with future sexual intercourse, dissatisfaction with genital appearance and fertility issues.



Acknowledging those functional issues, the results in the studies of this thesis were compared with outcome reported in the literature. Furthermore, postoperative complications were correlated with the degree of hypospadias, with the method of intervention, and with the boys' preoperative symptoms. In general, the symptoms of hypospadias depend on the degree of the condition. In this paper our focus has been the symptoms and signs that must be dealt with, i.e. urinary obstruction and debilitating curvature.

Another aspect of complications to hypospadias surgery is the postoperative risk of infection. Surgeons often administer prophylactic antibiotics, usually in a one-dose regimen preoperatively. The aim is to reduce the risk of a possible urinary tract infection (UTI) or wound infection related to the surgery or the malformation (16). Previous studies regarding the use of prophylactic antibiotics in conjunction with hypospadias repair show a difference of opinion (1,16–19). Due to increasing prevalence of antibiotic resistance it is important to investigate whether the incidence of UTIs is higher in hypospadias patients and what actions should be taken regarding antibiotic use associated with the operation (20).

Until 2012 the predominant method of hypospadias repair at our clinic was the Mathieu procedure (21). We then successively replaced this method with the TIP repair (22–24) which has become the most widely used technique worldwide. The reason for the change was the high complication rates in our series as well as in others reported in the literature (11).

The widely practised and established procedures to correct distal penile hypospadias are the Mathieu procedure with a perimeatal-based flap, and TIP urethroplasty. The Mathieu procedure was first described in 1932 and has been mainly used for coronal and subcoronal hypospadias (21). TIP urethroplasty was first described in 1994 and has been used to correct distal hypospadias (25). For both methods, complication rates have been reported to be 2%–13% (25–27). The most commonly reported serious complications after hypospadias surgery are urethral stricture and urethrocutaneous fistula, both of which require further surgical correcting. To date, there has been no consensus on the preferred choice between the Mathieu and TIP techniques, as well as on the short- and long-term outcomes of both procedures (27).

The most common postoperative complication after hypospadias surgery is that of a urethrocutaneous fistula (11,28,29). Speculations regarding the upcoming of fistulas have concerned postoperative local infections, increased pressure due to anastomotic narrowness or stricture, the effect of suturing manner and material as well as the surgeon's skills and choice of method (30,31). There are no reports on early signs, such as obstructive flow, that may signal a risk of the development of a fistula. Our

hypothesis was that a compromised uroflowmetry would signal a narrowness of the reconstructive area which would lead to increased pressure in the anastomoses. If too high a pressure, the neourethra might burst and the urine would take the easy way out and produce a fistula. Urinary diversion may then help to avoid this and, furthermore, if the hypothesis could be supported by data, an intervention dilating the urethral stricture may lead to a decreasing risk for the development of a fistula after the hypospadias reconstruction.



# Aim of project

The aim of the doctoral project was to evaluate surgical care and follow-up of hypospadias patients. The intention was to find ways to improve the surgical care and the situation of boys undergoing hypospadias repair. The specific aims of the included studies were:

## *Paper I*

To assess the rate of complications following hypospadias repair in a consecutive series of boys and the correlations of those complications with their preoperative symptoms, degree of hypospadias and method of operation. This study was conducted to shed light on the issue of whether all boys with any degree of hypospadias should undergo reconstruction.

## *Paper II*

To evaluate the frequency of UTI in boys with hypospadias pre- peri- and postoperatively in order to determine whether antibiotic prophylaxis for UTI is warranted when boys undergo reconstructive surgery for hypospadias.

## *Paper III*

To analyse if a change of surgical method affects the complication rate in hypospadias surgery. The Mathieu procedure was replaced by the TIP repair as the most favoured method to correct grade 1–2 hypospadias.

## *Paper IV*

To compare the two major complications, namely postoperative urethrocutaneous fistula and urethral stricture, between the Mathieu procedure and TIP repair method for distal hypospadias.

## *Paper V*

To see if the findings of routine postoperative urinary flow measurements could identify those boys prone to develop a fistula after surgery. If so, this could help in the identification and removal of the possible cause of the fistula and thereby improve outcome.



# Settings and patients

## Papers I, II, III and V

### *Patients*

All patients were treated at a tertiary centre of paediatric surgery, which conducts approximately 50% of hypospadias procedures in a region with a population of around 1.8 million inhabitants and the birth of 22,000 babies every year. As healthcare is free in the region, noncompliance due to socioeconomic factors is unlikely.

### *Surgeons and care*

The senior hypospadias surgeon at the hospital or a surgeon tutored by him, performed all the reconstructions. The surgeon who performed the operation was also responsible for the preoperative evaluation and work-up, as well as follow-up. All complications were handled by the same team of surgeons.

### *Patients collected for each clinical study*

The project was based on a routine follow-up programme that is connected to a local hypospadias register and database. Every boy consecutively undergoing hypospadias reconstruction at the tertiary centre of paediatric surgery was registered prospectively. Thus, the study groups comprised all boys who underwent primary surgery for urethral reconstruction during the period studied. All primary urethral reconstructions during the periods studied were included as summarised in Table 1.

Patients were identified from the register and information about patient characteristics, surgical procedures, complications and outcome of the postoperative urinary flow examinations was compiled retrospectively from the prospectively collected database.

**Table 1.** Summary of the number of boys included in the studies, degree of hypospadias and the periods studied.

| <b>Paper number</b> | <b>Hypospadias degree</b> | <b>Time period studied</b>  | <b>N</b>   |
|---------------------|---------------------------|---|--|
| <b>I</b>            | All degrees               | January 2011–April 2014   | 76   |
| <b>II</b>           | Degrees 1 and 2           | Early 2010 until the end of 2015  | 174 and<br>204 controls*                             |
| <b>III</b>          | Degrees 1 and 2           | The first period covers the years of 2010–2012 and the second the following 3 years 2013–2015** | 142<br>First period, n = 69<br>Second period, n = 73 |
| <b>V</b>            | Different degrees         | 2005–2018   | 73   |

\*The control group consisted of 204 boys, age 1–5 years, operated on for inguinal hernia.

\*\*The period was split into two equal halves mirroring the shift in paradigm.

Patients were identified from the register and information about patient characteristics, surgical procedures, complications and outcome of the postoperative urinary flow examinations was compiled retrospectively from the prospectively collected database.



# Methods

## Papers I, II, III and V

### Study design

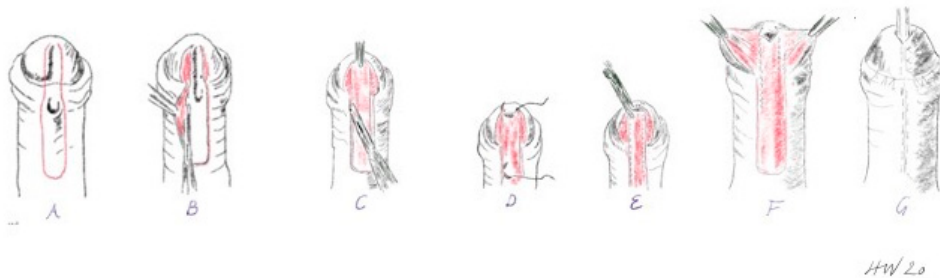
All the information was collected from the hospital registry for hypospadias patients and a control group was defined for Paper II.

### The surgical methods

Four different operative techniques were used, and all techniques are well established in the literature (9). The technique chosen for each boy was based upon the surgeon's choice and depended on the degree of hypospadias as described above, the individual prerequisite and the judgement of the surgeon. The Mathieu and "V" incision sutured meatoplasty (MAVIS) (21,32) was used for all degrees of hypospadias, whereas the TIP repair (25) was used for degrees 1 and 2. A Duckett reconstruction (33) was performed in one degree 2 patient. Two boys with degree 3 hypospadias were operated on using the Byars' two-stage reconstruction (34).

#### *Mathieu repair and MAVIS modification*

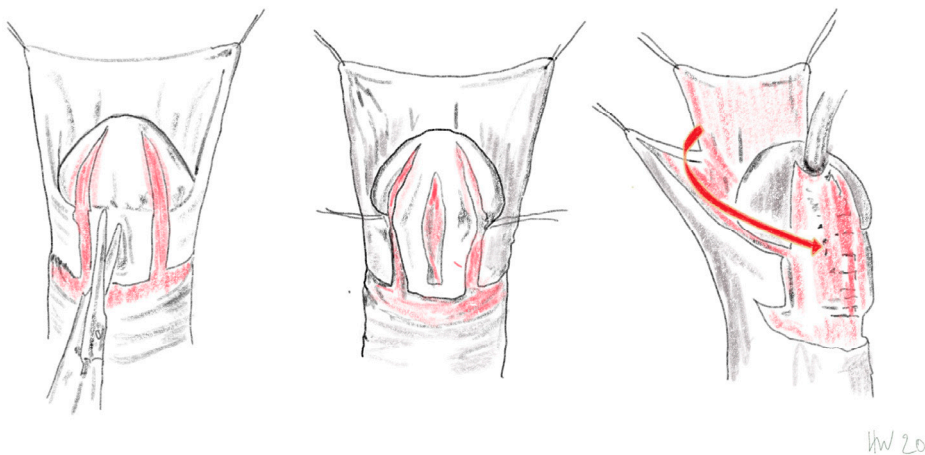
During the Mathieu procedure (21) a skin flap based towards the meatus is turned 180 degrees and sutured into incision on both sides of the glanular groove and along the tip of the penis. In the MAVIS (Mathieu and V-incision sutured meatoplasty) modification, a "V"-incision is made and excised at the apex of the flap with the purpose of achieving a vertical slit meatus (32). Curvature is corrected when present. The glans wings and ventral penile skin are then closed in the midline.



**Figure 3.** Mathieu perimeatal based flap.

*Tubularised incised plate repair (TIP)*

In TIP repair (22–25) a U-shaped skin incision is made along the edges of the urethral plate and the penis is degloved. The urethral plate is widened by a midline incision along its length and then tubularised over a stent. A pedicle of subcutaneous tissue is dissected from the ventral or dorsal penile skin and used to cover the neourethra. Finally, the glanular wings, mucosal collar and ventral penile skin are closed in the midline.

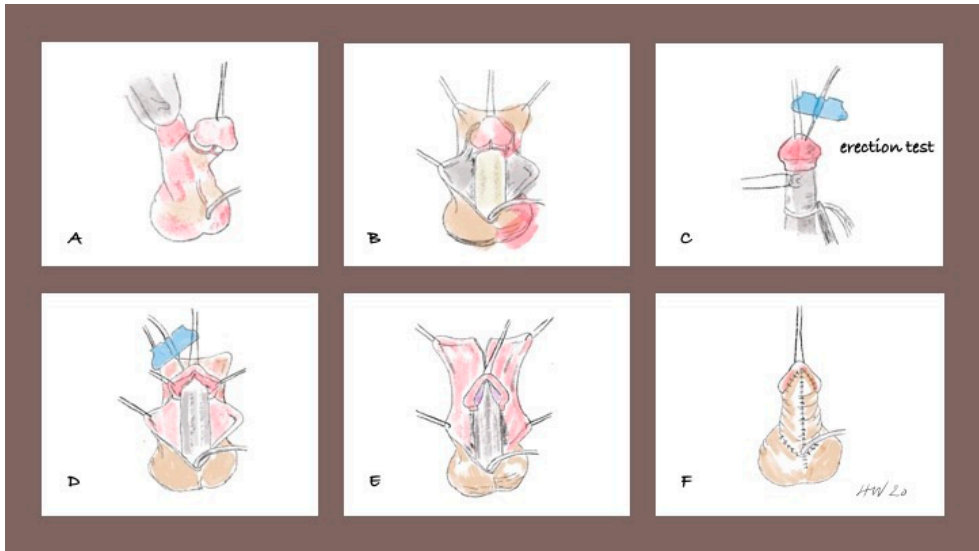


**Figure 4.** Tubularised incised plate urethroplasty (TIP).

*Byars’ two-stage repair*

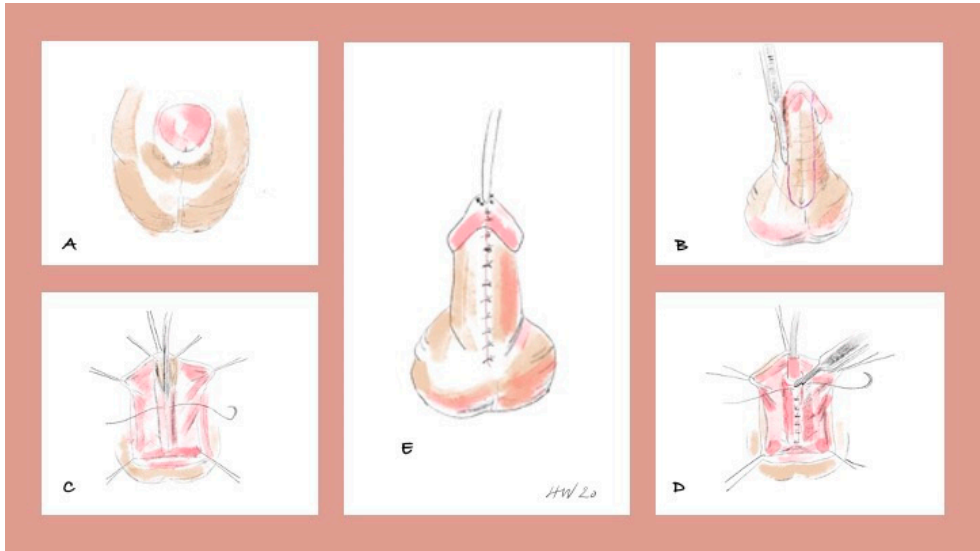
The Byars’ technique (34) starts with a straightening up procedure. A circumferential incision is made proximal to the coronal sulcus, the penile shaft is degloved and the curvature is corrected. Penile straightening and full removal of tension-creating

structures must be confirmed by means of the artificial erection test. The glans is either divided deeply in the midline to the tip or, if the mucosal groove is deep, this is preserved, and incisions are made just lateral to the groove on each side. The dorsal foreskin is unfolded carefully and divided in the midline. The most distal portion of the foreskin is rotated into the glanular cleft and sutured to the mucosa of the glans. A midline closure is performed, and the midline sutures catch a small portion of Buck's fascia. The bladder is drained with an 8-F Silastic Foley catheter for approximately 5–7 days.



**Figure 5.** Byar's two stage, stage one

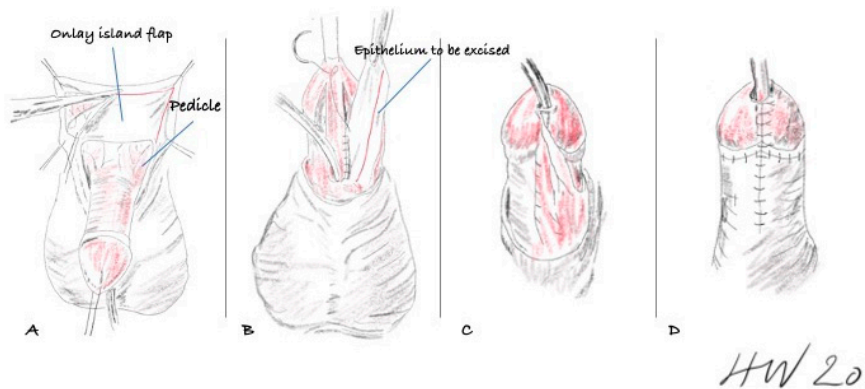
The second stage of the procedure is carried out 6–12 months later, when the tissues have usually softened sufficiently, and healing is complete. The previously transferred preputial skin is used to reconstruct the glans and urethra. A 16 mm-diameter strip is measured, extending to the tip of the glans. The strip is tubularised with a running subcuticular stitch all the way to the tip of the glans. The lateral skin edges are mobilised, and the remaining tissue is closed over the repair in at least two layers. A strip of skin (3–5 mm wide) is then de-epithelialised on one side to provide a raw surface of deep dermis. The medial edge of the shaved flap is brought across the buried urethroplasty and sutured to fascial tissue beneath the other flap.



**Figure 6.** Byar's two stage, stage two

### *Duckett reconstruction*

In the Duckett reconstruction (33), a straightening procedure is performed first. Then the ventral preputial flap is fanned out and the urethra outlined as a rectangle that is then incised and rolled into a tube over a catheter. An island flap is developed by dissection of subcutaneous tissue from the dorsal penile skin. A glans channel is created with scissors in a plane just above the corpora and all glans tissue is removed from the channel. The island flap urethra is spiralled ventrally, anastomosed to the proximal urethra and delivered to the tip of the glans. Finally, Byars' flaps, composed of dorsal penile skin, are transpositioned to the midline.



**Figure 7.** Duckett onlay island flap

## Perioperative regimen

### *Catheters*

For the TIP repairs, 8 Charrière (Ch) stents, allowing urinary dripping into the nappy were retained for 7 days. When a Mathieu or a Duckett plasty was performed, a suprapubic catheter 10 Ch was used for 7 days in all cases. For the tubularisation of the neourethra in the Duckett reconstructions, conventional “Foley™” catheters, 8 or 10 Ch, were used.

### *Suture technique*

For the urethral reconstruction, 5/0 or 6/0 polyglactin and polydioxanone sutures were used. They were sewn either with running or interrupted patterns according to the choice of the surgeon based on the local prerequisites.

### *Dressings*

The so-called chimney dressing used was the same for the patients in the Mathieu, Duckett and Byars’ I–II groups. This dressing consisted of a layer of transparent, flexible thin perforated polyurethane film embedded in a silicon wound contact layer, a layer of compressing gauze and a surrounding tape. These dressings resembled a chimney. The dressing used for the TIP operations consisted of a piece of hydrofibre dressing covering the suture line, transparent film wrapping, compression gauze bandage and fluffed gauze compresses. The dressings were all removed under general anaesthesia 1 week after the procedure.

### *Antibiotics*

The local guidelines stipulated one dose of prophylactic trimethoprim-sulfamethoxazole (co-trimoxazole) intravenously to all patients prior to surgery.

### *In hospital stay*

The boys who underwent Mathieu and TIP repair operations were discharged on day 3 after surgery. Their parents were instructed to keep the child in a supine or sitting position during the first week. When a Duckett repair or a Byars’ two-stage reconstruction was performed, the boys were hospitalised and immobilised in a wheelchair for a week.

### *Foreskin procedures*

In cases in which a TIP reconstruction was made, the parents might have requested a preputial reconstruction or a circumcision, either of which could be performed in the

same session (35). For the Mathieu procedure, we preferred to do these corrections in a secondary setting.

## Clinical follow-up and outcome

Patients were seen at the outpatient clinic 1 week after the reconstruction when the bandage and the catheter, whether suprapubic, a Foley or a dripping stent were removed. They were then called back to the out-patient clinic at 4 weeks and 2 and 6 months after the operation. In cases in which no complications occurred, a clinical examination was performed 1 year after the reconstruction. The boys were followed up according to the national guidelines at 5, 10 and 15 years of age (12).

During the visits, the patients were examined regarding urinary function including urinary flow measurements when applicable: i.e. if the patient was old enough and able to cooperate. The examinations of the surgical results focused on function, cosmetic appearance and complications such as fistulas, strictures, ruptures, postoperative infections, haematomas or bleeding, malfunctioning of catheters, and urinary retention.

We also registered the techniques used and the age at the time of the urethral reconstruction.

### *Main outcome measures*

Any complication calling for a reoperation, Clavien-Dindo IIIb (36), was considered as an outcome measure. This was any development of a fistula, rupture and/or stricture, during the period from the operative intervention until the endpoint of the study.

**Table 2.** Clavien-Dindo classification of complications (36).

| Grade             | Definition   |
|-------------------|--|
| <b>Grade I</b>    | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiologic interventions<br>Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside |
| <b>Grade II</b>   | Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included  |
| <b>Grade III</b>  | Requiring surgical, endoscopic or radiological intervention  |
| <b>Grade IIIa</b> | Intervention not under general anaesthesia   |
| <b>Grade IIIb</b> | Intervention under general anaesthesia   |
| <b>Grade IV</b>   | Life-threatening complication (including CNS complications) requiring IC/ICU management  |
| <b>Grade IVa</b>  | Single organ function (including dialysis)   |
| <b>Grade IVb</b>  | Multiorgan dysfunction   |
| <b>Grade V</b>    | Death of patient   |

### *Urethrocutaneous fistula*

A fistula between the urethra and penile skin is defined as a urethrocutaneous fistula and is a known complication of hypospadias repair.

### *Urethral stricture*

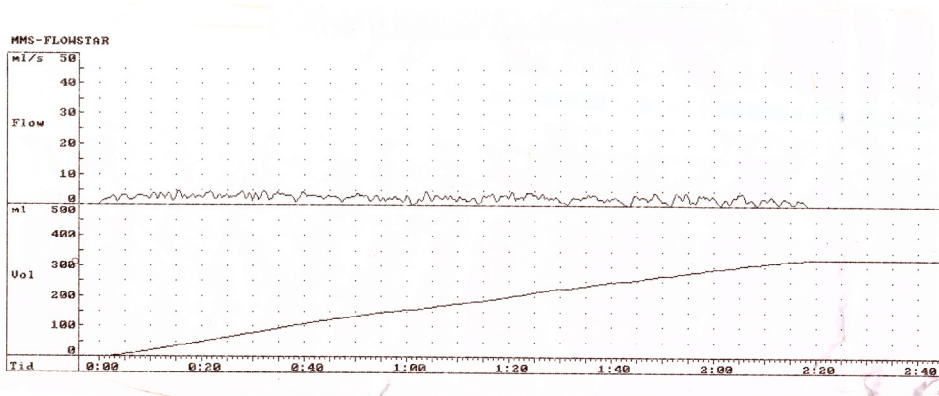
All urethral strictures that required reoperation under general anaesthesia were included. The localisation of the obstructive site, whether meatal, neourethral or anastomotic, was not considered important *per se* in the studies.

### *Postoperative infections*

In order to investigate the number of UTIs in each group, a regional database of bacteriological cultures was used to confirm infection in the urine cultures. Positive bacteria cultures before, during, and after the primary operation, were included in this study. All infections that occurred from birth until the primary urethral reconstruction were deemed preoperative, while a perioperative UTI was defined as one confirmed on the day of the operation and within 30 days after surgery. Postoperative infections included infections that occurred after 30 days from the day of surgery up until the end of this study (May 2015). For the hypospadias patients the following data were also registered: the use of prophylactic antibiotics, other congenital abnormalities of the genitourinary tract, and the degree of hypospadias.

### *Urinary flow measurements*

Urinary flow measurements were performed, at the earliest around 4 weeks postoperatively, according to standard method. Flow max, Q max (ml/s), voided volume (ml) and urinary flow pattern were measured. The urinary flow curve pattern was defined as normal if the curve was documented to be bell shaped, or as pathological if plateau shaped or uncoordinated corresponding to interrupted, staccato, spike-dome pattern.



**Figure 8.** Plateau-shaped uroflow curve.

The urinary flow analyses and frequency of fistula was evaluated for each surgical procedure. The urinary flow was then compared between boys with and without fistula.

## Paper IV: Meta-analysis

### *Search strategies*

The meta-analysis was conducted following the PRISMA guidelines (37). Using the keyword “hypospadias,” all literature published from January 1990 to January 2019 was searched in PubMed, EMBASE, and Cochrane databases. The inclusion criteria were: “hypospadias,” “Mathieu,” “tubularised incised plate repairs,” TIP,” “Snodgrass,” and “complications”, data that could be obtained from the paper. Cases were only included if the complications were identified and described with clarity in the paper. Filters were set for articles in English and those that included different age groups (i.e. infants, children, and adolescents).

First, all the abstracts were screened: all the studies that reported postoperative complications as an outcome after the Mathieu and TIP techniques were considered to meet the inclusion criteria. Then, the full articles were retrieved. All the eligible abstracts and articles were assessed independently by HW and EA for inclusion in the meta-analysis.



### *Inclusion criteria*

Included were all comparative studies who reported on urethrocutaneous fistula and urethral stricture after hypospadias repair by the two repair methods, the Mathieu and TIP techniques, on boys younger than 18 years.

### *Exclusion criteria*

Excluded were all non-original articles; those with cohorts smaller than 10 patients; those with a greater than 10:1 ratio between the two techniques; those that lacked reports on the two complications studied; those that reported overlapping data; and those in previously published articles. To reduce the risk of modification of the methods that might have influenced the rate of complications, studies with a time interval of greater than 20 years were excluded. Studies that included repeat operations were included when differentiating between repeat and primary interventions was not possible.

### *Complications*

Complications were defined according to Clavien-Dindo (36); studies with grade 3b complications of urethrocutaneous fistula and urethral stricture that required reoperation under general anaesthesia were included. The definition of stricture was decided subjectively by the surgeon/author or was measured objectively in correlation with the patient's age or postoperative time. Complications, such as infections and wound dehiscence, as well as cosmetics, were excluded from the analyses.

### *Data extraction*

The data extracted from the included articles were the study characteristics, such as authors, publication year, sample size, time span, surgical technique (Mathieu or TIP technique), and follow-up period, and patient characteristics, including age at surgery and degree of hypospadias. Specific information on postoperative complications was collected and analysed. In cases of uncertainty, events were not included.

### *Quality assessment*

The level of evidence and publication type was classified according to the Oxford CEBM, Levels of Evidence (38).

## Ethical considerations

This doctoral thesis was conducted according to the revised Helsinki Declaration of 1964 and the Good Clinical Practice (GCP) guidelines. It fulfilled the criteria of the general approval by the Regional Ethical Review Board (registration number 2010/49). The data were coded and de-identified. The included children were registered according to the regional demands on quality registry, number 01481271007173.

The study protocol was designed to meet the legislative documentation required by the country of origin. The intention-to-treat was the main analysis strategy and was applied to all boys. No protocols were exercised that would have required appropriate informed consent or approval of an institutional review board.

All evaluations, treatments, and procedures described in this report met the standard of care and were conducted at a tertiary centre for paediatric surgery. Since these data were collected retrospectively from a prospectively collected database, the treatment plan of each patient was not altered. The risk of harming the patients due to the study in any physical, social or psychological manner was non-existent.

The data were anonymised prior to calculations and are presented in such a manner that it is impossible to identify or link to any specific individual. Therefore, it was not necessary to obtain approval from the individual patient's guardians to conduct this study. It will not be possible to go back and trace or identify any of the participants. All information is in the patient's files.

## Statistical analysis

In **Paper I**, data were analysed by Fisher's exact probability test, two tailed, as well as non-parametric tests including the Mann–Whitney U test. A p-value of less than 0.05 was considered significant.

Sample size calculation was performed in **Paper II**. Because the value expected from the study group was 8% and that expected from the control group was 2%, the sample size provided was 71 for both groups.

The alpha error level or confidence level was 5%, corresponding to a 95% confidence interval (probability of incorrectly rejecting the null hypothesis that there is no difference in the percentage values).

Beta error level or statistical power (1-beta) was 50% (probability of incorrectly failing to reject the null hypothesis that there is NO difference in the percentage values, assuming no difference when a real difference exists).

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences). Fisher's exact probability test (two-tailed) was used for dichotomous variables and the Mann-Whitney U-test was used for continuous results.  $P < 0.05$  was considered to be statistically significant.

In **Paper III** a clinically significant relevance was set at a decrease in the complication rate by 20% units. The intention was to study independent cases and controls with one control(s) per case. Prior data indicated that the probability of exposure among controls is 0.3. If the true probability of exposure among cases is 0.1, we would need to study 72 case patients and 72 control patients to be able to reject the null hypothesis that the exposure rates for case and controls are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We used a continuity corrected chi-squared statistic or Fisher's exact test to evaluate the null hypothesis.

**Paper IV:** The Mantel-Haenszel method was used to calculate pooled odds ratio (OR) (39). Dichotomous variables were analysed by estimating the ORs with 95% confidence intervals (CIs).  $P$  values  $< 0.05$  were considered to be statistically significant. The RevMan 5.3 statistical package was used to conduct the meta-analysis (40).

**Paper V:** Prior data indicated that the probability of exposure among controls is 0.2. If the true probability of exposure among cases is 0.8, we would need to study seven case patients (developing fistula) and 35 control patients (without fistula) to be able to reject the null hypothesis that the exposure rates for case and controls are equal with probability (power) 0.8. The Type I error probability associated with this test of the null hypothesis is 0.05. A continuity-corrected chi-squared statistic or Fisher's exact test was used to evaluate the null hypothesis (41).



# Results

## Paper I

Seventy-six boys underwent primary hypospadias repair during a 40-month period. Their median age (range) at the time of repair was 3 (0–8) years, and the median (range) follow-up period was 19 (1–40) months. No boy was lost to follow-up. The preoperative status and evaluations of function are summarised in Table 3.

**Table 3.** Preoperative clinical evaluations of the 76 boys with hypospadias.

|  | Anatomical malformation      |               | Penis function                         |                                       |
|--|------------------------------|---------------|--|---------------------------------------|
|  | Degree of hypospadias<br>1–3 | Number<br>(n) | Expected micturition<br>problem in (n) | Expected copulation<br>problem in (n) |
| <b>Ventral<br/>curvature<br/>(n = 10)</b>    | <b>1</b>                     | 1             | 1                                      | 1                                     |
|  | <b>2</b>                     | 6             | 4                                      | 6                                     |
|  | <b>3</b>                     | 3             |  | 3                                     |
| <b>No ventral<br/>curvature<br/>(n = 66)</b> | <b>1</b>                     | 22            | 12                                     |                                       |
|  | <b>2</b>                     | 41            | 20                                     |                                       |
|  | <b>3</b>                     | 3             | 1                                      |                                       |
| <b>Meatal<br/>stenosis</b>                   | 1-3                          | 38            | 38                                     |                                       |

Ten of the patients were described as having curvatures that might have interfered with future sexual function and this observation prompted surgery. Nineteen had meatotomy performed prior to the urethral reconstructions, and another 19 had meatotomy performed as a part of the urethral reconstruction. Uroflowmetry examinations were performed in 30 boys.

The stenosis was defined as difficulty in urinating. Difficulties were defined as frequent micturition, prolonged urination, a thin stream, and difficulties starting urinary flow, keeping the flow going, difficulties in directing the stream into the toilet, spraying of the urinary stream, and straining or arching of the back during voiding. These clinical findings were supported by uroflowmetry measuring the volume, the speed with which it is released, and duration of urine released from the body. Furthermore, bladder ultrasound was used to detect urinary retention.

The most preferred method of reconstruction was the Mathieu procedure, which was used for any degree of hypospadias and in 13, 27 and 3 boys with degrees 1, 2 and 3, respectively. The TIP method was used for degree 1 in 10 boys and for mild degree 2 in 18 boys.

Table 4 summarises the postoperative complications that were correlated with the meatal location. The numbers of complications did not differ significantly between the groups with different degrees of hypospadias.

**Table 4.** The complications of hypospadias including fistulas, rupture and other complications and their correlations with the meatal locations described using the different degrees of hypospadias.

| Hypospadias degree    | 1  | 2  | 3 | p-value* |
|-----------------------|----|----|---|----------|
| <b>n</b>              | 23 | 47 | 6 |          |
| <b>Complications:</b> |    |    |   |          |
| - <b>Fistulas</b>     | 5  | 14 | 3 | 0.48     |
| - <b>Ruptures</b>     | 2  | 1  | 1 | 0.24     |
| - <b>Others</b>       | 2  | 9  | 0 | 0.56     |

\*The Freeman-Halton extension of Fisher's exact test.

Table 5 shows the complications and methods of repair. In the Mathieu group, 18 (42%) had a fistula or rupture that necessitated reoperation. The corresponding number for the TIP procedures was 4 (15%), which was significantly lower.

**Table 5.** The method of operation correlated with the postoperative complications\*.

|                             | Total    | TIP<br>(n = 28) | Mathieu<br>(n = 43) | Duckett (n = 1)<br>Byars (n = 4) | p-value* |
|-----------------------------|----------|-----------------|---------------------|----------------------------------|----------|
| <b>Fistulas</b>             | 22 (29%) | 3 (11%)         | 15 (35%)            | 4 (80%)                          | 0.02     |
| <b>Ruptures</b>             | 4 (5%)   | 1 (4%)          | 3 (7%)              |                                  | 0.28     |
| <b>Urethral stricture</b>   | 1 (1%)   | 1 (4%)          | 0                   | 0                                | 0.38     |
| <b>Infections</b>           | 2 (3%)   | 0               | 2 (5%)              | 0                                | 0.38     |
| <b>Haematoma/bleeding</b>   | 4 (5%)   | 3 (11%)         | 1 (2%)              | 0                                | 0.13     |
| <b>Catheter malfunction</b> | 2 (3%)   | 2 (7%)          | 0                   | 0                                | 0.14     |
| <b>Urinary retention</b>    | 1 (1%)   | 0               | 0                   | 1 (20%)                          | 1.0      |
| <b>p-value**</b>            |          | 0.16            | 0.21                | 0.01                             |          |

\* Fisher's exact test

\*\*Mann-Whitney U Test

The clinical symptoms that preceded the repairs were correlated with the postoperative complications. There were no differences regarding the postoperative complications.

## Paper II

The results of the data collection on the study group of 174 boys who underwent primary hypospadias surgery regarding degree, other congenital malformations of the urogenital tract, and prophylactic antibiotics are summarised in Table 6. The most common characteristics were degree 2 hypospadias and no other congenital urogenital malformations in addition to hypospadias. Of the boys who suffered a UTI, 77% had other congenital malformations of the genitourinary tract ( $p = 0.02$ ), either hydrocoele or undescended testis.

**Table 6.** Data on 174 boys who underwent hypospadias surgery regarding degree, other congenital urogenital malformations, and prophylactic antibiotics.

| <b>Hypospadias patients</b>              |     | <b>(n = 174)</b> |
|--|-----|------------------|
| Hypospadias degree 1 (glanular)          | 44  | (25%)            |
| Hypospadias degree 2 (penile)            | 109 | (63%)            |
| Hypospadias degree 3 (proximal)          | 18  | (10%)            |
| No degree recorded                       | 3   | (2%)             |
| Other congenital urogenital malformation | 29  | (17%)            |
| Prophylactic antibiotics                 | 116 | (67%)            |

The control group comprised 204 boys who underwent inguinal hernia repair. The median age at operation and the duration of follow up did not differ between the groups.

There were significantly more boys with UTIs in the hypospadias group, compared with the controls.

The UTIs contracted peri-operatively and up to 30 days postoperatively did not differ between the study group and the control group. This finding of no difference in the 30-day postoperative period held true even after excluding the boys receiving preoperative antibiotic prophylaxis.

**Table 7.** Urinary tract infections in the study group of 174 boys operated on for hypospadias compared with a control group of 204 boys who underwent inguinal hernia repair. Values are presented as median (range), absolute number (n) and percentage (%) of patients.

|                                       | <b>Study group:<br/>Hypospadias<br/>(n = 174)</b> | <b>Control group:<br/>Inguinal hernia<br/>(n = 204)</b> | <b>p-value</b> |
|---------------------------------------|---|---|----------------|
| <b>Age (years)</b>                    | 4 (1–8)   | 3 (1–5)   | 0.08*          |
| <b>Follow-up (years)</b>              | 5 (0.5–15)  | 4 (1–8)   | 0.73*          |
| <b>Urinary tract Infection, n (%)</b> | 13 (7.5%)   | 3 (1.5%)  | <0.01**        |
| <b>Preoperatively</b>                 | 3 (2%)  | 2 (1%)  | 0.66**         |
| <b>Perioperatively***</b>             | 1 (1%)  | 0   | 0.10**         |
| <b>Postoperatively</b>                | 9 (5%)  | 1 (0.5%)  | 0.03**         |

Values are presented as median (range), absolute number (n) and percentage (%) of patients.

\*Mann-Whitney U-Test; \*\*Fisher's exact test \*\*\*within 30 days postoperative

### Paper III

The third paper comprised 142 boys going through hypospadias repair during two equally long time periods. There were 69 and 73 boys in the first and second period, respectively. In the first period 50 (72%) of the boys underwent the Mathieu procedure compared to the second period where only 19 (26%) were selected for this method. The corresponding numbers for TIP repair were 19 (28%) and 54 (74%), respectively. In the first period 35 (51%) of the boys required another operation compared to only 15 (21%) in the second,  $p < 0.01$ , Table 8.

For obvious reasons the duration of follow up was longer in the first period. The duration of the follow-up was also influenced by emigration to other countries and in some cases caretaking at another hospital in the region or by their own parents if they had urological competence. The most common postoperative complication was an urethrocutaneous fistula. The time of the reoperations was median 15 months (range 2–72 months) after primary repair and was not significantly different between the groups from the two periods.



**Table 8.** The rate of complications in 142 boys undergoing hypospadias repair.

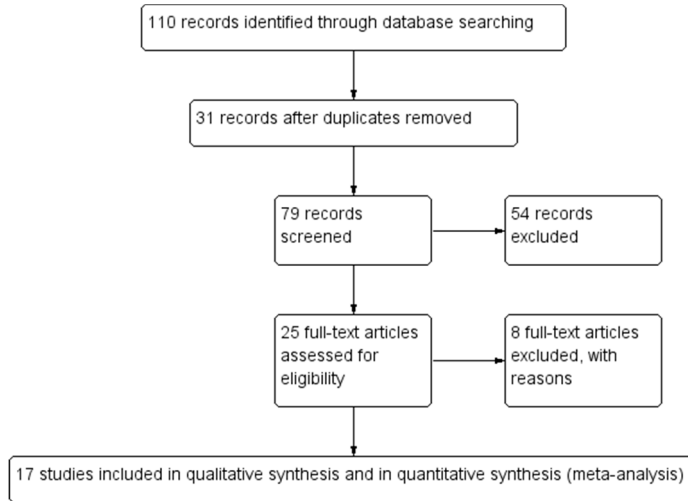
|   | 2010–2012<br>n = 69 | 2013–2015<br>n = 73 | Total<br>n = 142 | p-value*            |
|---|---------------------|---------------------|------------------|---------------------|
| <b>Complications, n (%)</b>   | 35 (51%)            | 15 (21%)            | 50 (35%)         | <0.01 <sup>a</sup>  |
| <b>Type of complication</b>   |                     |                     |                  |                     |
| • <b>Fistula</b>  | 24 (35%)            | 10 (14%)            | 34 (24%)         | < 0.01 <sup>a</sup> |
| • <b>Rupture</b>  | 11 (16%)            | 1 (1%)              | 12 (8%)          | < 0.01 <sup>a</sup> |
| • <b>Stricture</b>  | 0                   | 4 (5%)              | 4 (3%)           | 0.12 <sup>a</sup>   |
| Degree 1**  |                     |                     |                  |                     |
| • <b>Mathieu</b>  | 19 (9)              | 6 (0)               | 25 (9)           |                     |
| • <b>TIP</b>  | 8 (4)               | 13 (1)              | 21 (5)           | 0.02 <sup>a</sup>   |
| Degree 2**  |                     |                     |                  |                     |
| • <b>Mathieu</b>  | 31 (17)             | 13 (7)              | 44 (24)          |                     |
| • <b>TIP</b>  | 11 (5)              | 41 (7)              | 52 (12)          | <0.01 <sup>a</sup>  |
| <b>Number of:</b>   |                     |                     |                  |                     |
| <b>Mathieu (complications)</b>  | 50 (26=52%)         | 19 (7=37%)          | 69 (33=48%)      | 0.46 <sup>a</sup>   |
| <b>TIP (complications)</b>  | 19 (9=47%)          | 54 (8=15%)          | 73 (17=23%)      | 0.03 <sup>a</sup>   |
| <b>Duration of follow-up, months, median (range)</b>                    | 29 (3–73)           | 13 (1–53)           | 19 (1–73)        | <0.05 <sup>b</sup>  |
| <b>Timing of complications after the reconstruction, months (range)</b> | 2 (0–52)            | 2 (1–19)            | 2 (0–52)         | 0.41 <sup>b</sup>   |
| <b>After: 6 months</b>  | 25                  | 9                   | 34               | <0.01 <sup>a</sup>  |
| <b>≤1 year</b>  | 5                   | 5                   | 10               | 1 <sup>a</sup>      |
| <b>&gt;1 year</b>   | 5                   | 1                   | 6                | 0.11 <sup>a</sup>   |

The numbers in brackets are complications, i.e. a fistula, a rupture or a stricture

\*Statistical method: <sup>a</sup>Fisher's exact test and <sup>b</sup>Mann–Whitney U test

## Paper IV

A literature search for “hypospadias AND Mathieu AND tubularised incised plate (TIP) repair AND children” provided 110 studies. These 110 abstracts were screened, of which 17 studies met the eligibility criteria (Figure 6). After collecting the information from the full text articles, all 17 studies fulfilled the criteria to be included in the final meta-analysis (Table 9). The overall CEBM criteria ranged from 1b to 2b, i.e. from RCT to cohort study (38). Search for hypospadias and meta-analysis revealed seven publications, but none of these were relevant for this study.



**Figure 9.** Flowchart of the process to search for articles that compared the complications after hypospadias reconstruction using the Mathieu and TIP repair methods.

**Table 9.** A summary of the studies included in this meta-analysis.

| References               | Year | Level of evidence | Mathieu    | TIP        | Mathieu    | TIP       |           |           |
|--------------------------|------|-------------------|------------|------------|------------|-----------|-----------|-----------|
|                          |      |                   | n          | n          | Fistulae   | Stricture | Fistulae  | Stricture |
| <b>Aminsharifi (42)</b>  | 2008 | 1b**              | 20         | 20         | 0 (0%)     | 0 (0%)    | 2 (10%)   | 5 (25%)   |
| <b>Anwar-ul-haq (43)</b> | 2006 | 2b***             | 45         | 45         | 7 (16%)    | 3 (7%)    | 3 (7%)    | 2 (4%)    |
| <b>Bae (44)</b>          | 2014 | 2b                | 13         | 25         | 1 (8%)     | 0 (0%)    | 6 (24%)   | 1 (4%)    |
| <b>Chrzan (45)</b>       | 2007 | 2b                | 25         | 26         | 1 (4%)     | 1 (4%)    | 17 (65%)  | 1 (4%)    |
| <b>Elganainy (46)</b>    | 2010 | 1b                | 64         | 37         | 5 (8%)     | 0 (0%)    | 3 (8%)    | 5 (14%)   |
| <b>Guo (47)</b>          | 2004 | 1b                | 43         | 36         | 11 (26%)   | 1 (2%)    | 3 (8%)    | 2 (6%)    |
| <b>Hamid (48)</b>        | 2014 | 1b                | 48         | 52         | 6 (13%)    | 4 (8%)    | 3 (6%)    | 3 (6%)    |
| <b>Imamo lu (49)</b>     | 2003 | 2b                | 54         | 56         | 4 (7%)     | 2 (4%)    | 4 (7%)    | 5 (9%)    |
| <b>Karabulut (50)</b>    | 2008 | 2b                | 9          | 4          | 5 (56%)    | 0 (0%)    | 2 (50%)   | 1 (25%)   |
| <b>Moradi (51)</b>       | 2005 | 1b                | 18         | 15         | 1 (6%)     | 0 (0%)    | 2 (13%)   | 1 (7%)    |
| <b>Nezami (52)</b>       | 2010 | 1b                | 33         | 21         | 1 (3%)     | 0 (0%)    | 1 (5%)    | 1 (5%)    |
| <b>Oswald (53)</b>       | 2000 | 1b                | 30         | 30         | 2 (7%)     | 1 (3%)    | 0 (0%)    | 0 (0%)    |
| <b>Oztorun (54)</b>      | 2017 | 2b                | 331        | 161        | 38 (11%)   | 1 (0%)    | 23 (14%)  | 1 (1%)    |
| <b>Samore (55)</b>       | 2006 | 1b                | 10         | 10         | 2 (20%)    | 1 (10%)   | 2 (20%)   | 1 (10%)   |
| <b>Ugras (56)</b>        | 2006 | 2b                | 34         | 20         | 5 (15%)    | 0 (0%)    | 3 (15%)   | 1 (5%)    |
| <b>Winberg (57)</b>      | 2016 | 2b                | 69         | 73         | 24 (35%)   | 0 (0%)    | 10 (14%)  | 4 (5%)    |
| <b>Yildiz (58)</b>       | 2010 | 2b                | 16         | 79         | 2 (13%)    | 1 (6%)    | 6 (8%)    | 3 (4%)    |
|                          |      | <b>Total:</b>     | <b>862</b> | <b>710</b> | <b>115</b> | <b>15</b> | <b>90</b> | <b>37</b> |

TIP: tubularised incised plate

\*\*1b: Randomised controlled trial (RCT)

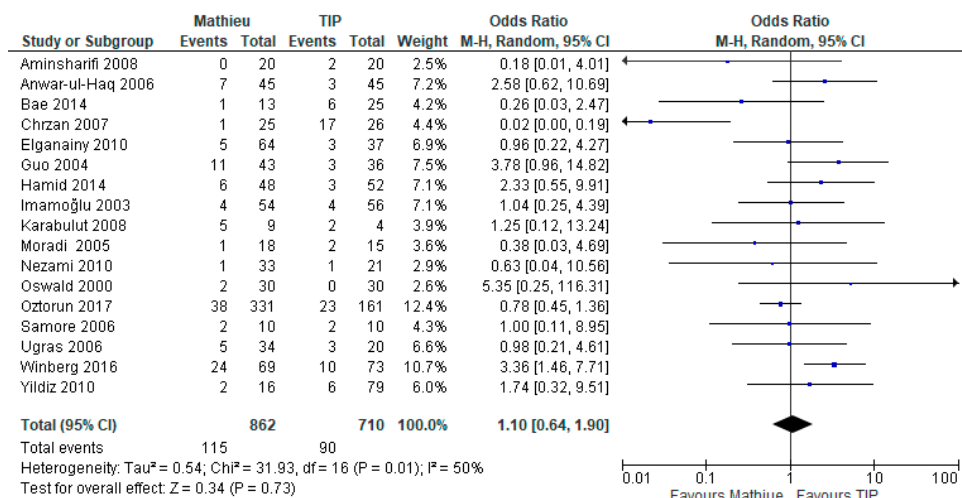
\*\*\*2b: Cohort study

### Study characteristics

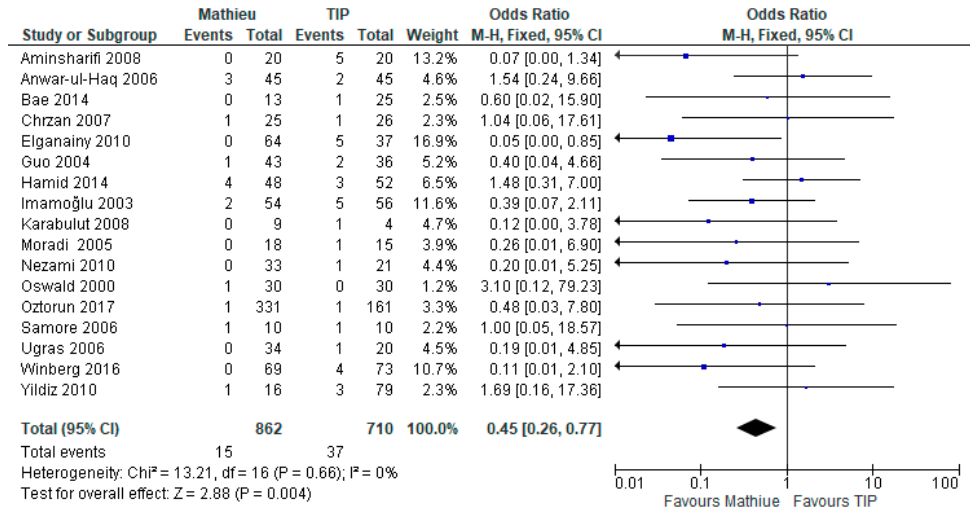
A total of 1572 patients (range, 13–492 patients per study) were included in the meta-analysis. Of these, 862 (55%) had undergone surgery with the Mathieu procedure and 710 (45%) with TIP repair. Some local variations in the surgical methods were noted during the data extraction, although the general principles of the methods were equal and allowed comparison. Data on age at surgery, weight, and indication for the hypospadias repair were not provided in detail in all the studies; therefore, these were not included in the current analysis. A summary of the characteristics of the included studies is shown in Table 10.

### Frequencies of fistula and stricture

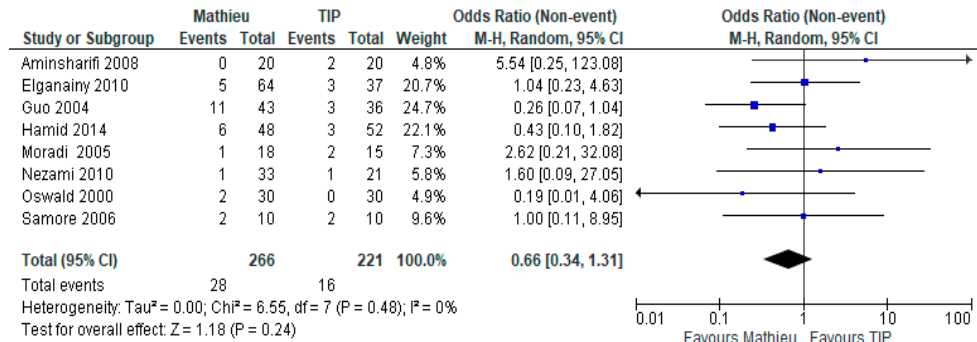
Overall, 259 of 1572 (16%) boys developed complications of fistula or urethral strictures that required reoperation. Specifically, these complications occurred in 130 of 862 (15%) patients who underwent the Mathieu procedure and in 129 of 710 (18%) patients who underwent TIP repair. Urethrocutaneous fistula was less frequent with the Mathieu procedure than with TIP repair in eight studies; less frequent with TIP repair than with the Mathieu procedure in seven studies; and similar between the two methods in three studies. Urethral stricture was less frequent with the Mathieu procedure than with TIP repair in 11 studies; less frequent with TIP repair than with the Mathieu procedure in three studies; and similar between the two methods in three studies.



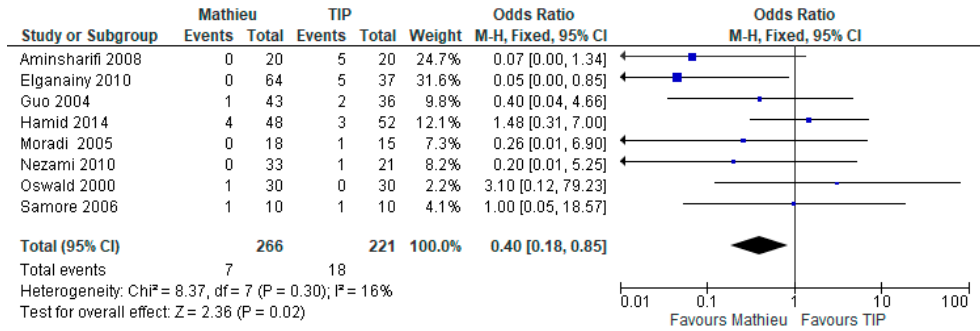
**Figure 10.** Forest plot of the comparison between the Mathieu procedure and TIP repair methods for hypospadias reconstruction, in terms of fistula formation.



**Figure 11.** Forest plot of the comparison between the Mathieu procedure and TIP repair methods or hypospadias reconstruction, in terms of postoperative strictures.



**Figure 12.** Forest plot of the comparison between the Mathieu procedure and TIP repair methods for hypospadias reconstruction, in terms of fistula formation among the RCTs.



**Figure 13.** Forest plot of the comparison between the Mathieu procedure and TIP repair methods for hypospadias reconstruction, in terms of postoperative strictures among the RCTs.

## Paper V

The background data did not show any significant differences between the boys operated on using different methods of hypospadias repair (Table 10).

The age and the time of follow-up with urinary flow examinations in the group of boys with postoperative fistula, versus those without, did not differ significantly which is displayed in Table 12.

The urinary flow measurement results differed significantly between the three reconstructive methods used at the centre, Table 11. The maximal flow rate as well as the appearance of the curve were closer to normal after the Mathieu procedure.

The results of the urinary flow rate in the group of boys developing a fistula after hypospadias repair versus those who did not are summarised in Table 13. No significant difference was disclosed. The urinary flow measurements were performed at the earliest 3 weeks' postoperatively. All but one was performed at the time of discovery of the fistula.

**Table 10.** Data on 73 boys who underwent hypospadias surgery regarding degree, urethrocutaneous fistula other congenital urogenital malformations, and prophylactic antibiotics.

|   | <b>Total</b> | <b>Byars'</b> | <b>Mathieu</b> | <b>TIP</b> | <b>p-value</b> |
|---|--------------|---------------|----------------|------------|----------------|
| <b>n (%)</b>                            | 73           | 3 (4%)        | 19 (26%)       | 51 (70%)   |                |
| <b>Age at operation, months (range)</b> | 50 (14–92)   | 47 (14–49)    | 52 (18–77)     | 50 (17–92) | 0.79*          |
| <b>Grade 1 (distal)</b>                 | 20 (27%)     |               | 4              | 16         | 0.89**         |
| <b>Grade 2 (shaft)</b>                  | 50 (68%)     | 1             | 15             | 34         | 0.78**         |
| <b>Grade 3 (proximal)</b>               | 3 (4%)       | 2             | 0              | 1          | 0.01**         |
| <b>Urethrocutaneous fistula</b>         | 13 (18%)     | 1             | 6              | 6          | 0.22**         |
| <b>Other congenital malformation***</b> | 8 (11%)      | 0             | 2              | 6          | 1.00**         |
| <b>Antibiotics</b>                      | 65 (89%)     | 3             | 14             | 44         | 0.95**         |

\*Mann-Whitney U-Test (two tailed)

\*\*The Fisher exact probability test for two-rows by three-column contingency table, the Freeman-Halton extension

\*\*\*The other congenital urogenital malformations (n) included: inguinal hernia (6), undescended testis (1), pelvis-ureteral junction (PUJ) obstruction (1), renal agenesis (1), vesicoureteral reflux (VUR) (1), persistent Müllerian structures in disorders of sexual differentiation (DSD) conditions (1) as well as renal dysplasia (1).



Figure 14. Uroflowmetry, the "receipt toilette".

**Table 11.** The urinary flow measurements showing the Q max, volume and the curve formation correlated to the technique of operation. Bell-shaped suggested a normal curve while plateau-shaped suggested obstruction.

| Parameters    |                        | Byars n = 3 | Mathieu n = 18 | TIP n = 51  | p-value* |
|---------------|------------------------|-------------|----------------|-------------|----------|
| <b>n = 73</b> |                        | 2 of 3      | 13 of 19       | 28 of 51    |          |
| <b>Qmax 1</b> | Median (range)<br>ml/s | 6 (5–7)     | 10 (8 - 15)    | 6 (2–18)    | <0.01*   |
| <b>Volume</b> | Median (range)<br>ml   | 23 (19–26)  | 130 (56–380)   | 67 (12–257) | 0.06*    |
| <b>Curve</b>  | Bell-shaped            | 2           | 12             | 15          | 0.02*    |
|               | Plateau shaped****     | 0           | 0              | 13          |          |

The group of patients operated on using the Byars' technique was too small (< 5) and was not included in the statistics.  
\*Mann Whitney U-test.

**Table 12.** Urinary flow measurements in boys with postoperative uretero-cutaneous fistula, n = 13, versus without, in the study group of 73 boys operated on for hypospadias.

| After surgery for hypospadias   | With fistula*         | Without fistula | p-value * |
|---|-----------------------|-----------------|-----------|
| <b>Patients (n)</b>   | 13                    | 60              |           |
| <b>Age, years (range)</b>   | 4 (1–6)               | 4 (1–8)         | 0.21      |
| <b>Duration of time from reconstruction to urinary flow measurements, months (range)</b>              | 2 (13 days–31 months) | 1 (1–7)         | 0.76      |
| <b>Duration of time from reconstruction to uretero-cutaneous fistula complication, months (range)</b> | 2 (0–11) **           |                 |           |
| <b>Follow-up time after last surgery (months)</b>   | 75 (54–184)           | 69 (30–176)     | 0.25      |

\*Mann-Whitney U-Test (two tailed).

\*\*All but four fistulas had appeared before the first flow measurement.

**Table 13.** Urinary flow rate and flow pattern after hypospadias reconstruction in 73 patients.

| Postoperative uroflow parameters        | With fistula<br>n = 13 | Without fistula<br>n = 60 | p-value |
|---|------------------------|---------------------------|---------|
| <b>Q max (ml/s), mean (range)</b>       | 11 (4–16)              | 8 (3–74)                  | 0.25*   |
| <b>Voided volume (ml), mean (range)</b> | 94 (35–171)            | 94 (0–270)                | 0.98*   |
| <b>Urinary flow pattern:</b>            |                        |                           |         |
| • <b>Bell shaped (%)</b>                | 9 (69%)                | 41 (68%)                  | 0.42**  |
| • <b>Plateau shaped</b>                 | 3 (23%)                | 18 (30%)                  |         |

\*Mann-Whitney U-test;

\*\*Fisher's exact test (two-tailed).



# Discussion

## **Complications and correlation with symptom, degree and method of operation (Paper I)**

*Should all boys with any degree of hypospadias undergo reconstruction?*

Of course, this is a provocative question. But nevertheless, in clinical practice the paediatric surgeon notes that small boys seldom have any subjective problems from their hypospadias. So, the mean objective for surgical treatment in childhood is to prevent problems later in life. It is not obvious how a conclusion made early, at the recommended time for hypospadias repair, can be drawn with respect to overall function. According to most authors, judgements concerning voiding and erection in adult life have to wait until after puberty (59,60).

The outcome measurements in this study included the frequency of postoperative complications that correlated with preoperative symptoms and/or signs, the degree of hypospadias and the various operative interventions. The results can only explain whether there were differences between the different parameters studied. It cannot indicate differences between operations and non-operations because all the boys underwent operative interventions. Thus, the results only add indirectly to information to the research question above. Operations on boys without symptoms and/or signs cause complications with a frequency that is comparable to those for which an operative intervention is assumed necessary.

Due to the findings, when penile function is normal, the Hippocratic principle of not harming, by not performing surgery, should be considered seriously.

The frequency of complications in our series was high: more than every third boy needed an extra procedure under general anaesthesia (Clavien-Dindo IIIb). The results were insignificantly different from those that have previously been described in comparable reports collected from the literature over the last few years (30,42,46,61,62).

However, there are reports of significantly worse findings than ours (63). The reasons for a high frequency of complications are probably multifactorial, but taking into account other explanations, the following are worth mentioning.

### *Type of study and compliance with follow up*

In our study, data were gathered prospectively, although analysed retrospectively. To provide better insights into various questions, including the true complication rate after different methods of repair, data should be registered prospectively (2). Promising initiatives in this direction are the Dutch hypospadias database and SWEAPS, the Swedish national quality registry. In the latter all boys with hypospadias referred to a tertiary centre in Sweden will be registered (64). With a longer follow up time, the rate of complications might increase since complications might be discovered as late as at post-pubertal examinations (60).

### *Surgeons' experience and skills*

Unpublished data from the Dutch hypospadias database presented at the NBUF (Nordic Paediatric Urologist Association) meeting some years ago, stated that the surgeon's skill and experience was central in the outcome of hypospadias surgery. When the surgeon chooses to operate, the interpretation of the degree of the hypospadias might differ between different surgeons, e.g. underestimation due to concomitant curvature. To minimise this issue, the group of boys described in Paper 1 was evaluated based on the consensus between the two operating surgeons.

The surgeon also chooses the age at reconstruction. This is still a subject of debate (11). The age in our series was uniform, but certainly higher than recommended. Globally, paediatric surgeons advocate surgery between 6 and 18 months and this is commonly adopted (65). The rationale for this is mainly psychological, i.e. claimed gender unawareness and that the boy would not be able to remember the intervention. The limitation in the lower age range is the penile size and increased anaesthetic risk. On the other hand, there are reports that state that age at surgery does not increase the risk of urethroplasty complications (66).

The surgeon then chooses the method of repair and for this a standardisation is still missing in the literature (2). Although too small a group to reach a conclusion in our small series, one may have concerns that the wrong operations have been performed for the more proximal hypospadias and those boys with a significant curvature. This is expressed by the high (50%) fistula rate in boys with curvature. These boys should probably not have had a single-stage repair. Acknowledging this, in the literature repair for proximal hypospadias still carries a high complication rate.

When the surgeon starts to operate, his or her skill and experience are crucial for the outcome (2). In Paper 1 we describe the results of two experienced and dedicated surgeons who operated on the boys. Different surgeons use different suturing material and suturing technique; they also prescribe different schemes of antibiotics. Beyond

this, the use of catheters and their route can vary, the dressings, and the mobilisation plan, etc, differ between centres. There can be day-case fast-track surgery or in-hospital stays of up to 3–5 days. For all these aspects there is still no consensus (11).

### **Risk of UTI in boys with hypospadias (Paper II)**

The results reveal significantly more UTIs in a group of boys with hypospadias undergoing reconstructive surgery compared with a control group of boys operated on for an inguinal hernia. Many of the boys with hypospadias and positive urine cultures, regardless of when the infection occurred, also had another congenital urogenital malformation. Whether the other congenital malformations do have any impact on the frequency of UTI remains to be studied.

The physiological characteristics of children with a UTI are quite different from adults. Young children with UTIs may have a fever, poor appetite, vomiting, or no symptoms at all. In addition, the children have problems expressing themselves. To determine that the symptomatic UTIs really exist, bacteriological culture of urine is necessary, as performed in our study.

Previous studies have also investigated the role of antibiotic prophylaxis in this context. The opinions vary among the different studies. Two older studies (19,67) encourage the use of prophylactic treatment, while more recent ones (16,68), find it unnecessary. They are all case-control studies where one group received prophylactic antibiotics and the other did not. In the older studies (19,67), urine cultures were performed regularly on all patients, regardless of whether symptoms of an infection were present. They observed a higher incidence of UTIs in the group where no prophylactic antibiotics were given; thus, the use of prophylaxis was recommended (19,67). The more recent studies (16,68), only performed a urine culture when the patient presented with symptoms, such as high fever, irritability, or pain while voiding. They could not identify a difference in the incidence of symptomatic UTIs between their two groups and opposed the use of prophylaxis in this respect (16,68).

We only registered symptomatic UTIs confirmed by positive urine cultures. Therefore, our study design is more like the latter two studies mentioned above (16,68). If we had performed the urine cultures in all patients, the number of positive results would probably have increased and resembled the results of the early two studies (19,67). In order to proceed with this issue, one needs to decide whether asymptomatic UTIs should be classified as equally severe as symptomatic ones. Previous studies state that patients with asymptomatic bacteriuria should not be treated with antibiotics, except for pregnant women and patients undergoing urological interventions (69). According

to these guidelines, standardised urine cultures should be performed for all hypospadias patients in order to diagnose and treat these asymptomatic infections.

We chose to collect the control group from a cohort of boys undergoing an operative intervention for inguinal hernia. One might argue that a population-based control group would be more appropriate. However, we considered that a group of boys also undergoing an operative intervention at the same hospital would be the most appropriate control group, being exposed to similar conditions.

The frequency of UTIs must be compared with that of the general population. It has been estimated that 1% of prepubertal boys are diagnosed with UTIs (70). Using that figure in comparison with the boys with hypospadias, instead of using the boys undergoing an inguinal hernia operation, would not change the conclusions in this study.

Whether or not boys with hypospadias have a higher incidence of UTIs has been debated. Wehbi et al stated that the incidence of recurrent UTIs in hypospadias patients is higher over time (1.9%) than that of boys without this malformation (0.1–0.2%), with a median follow-up time of 6.5 years (18). This is in accordance with our postoperative results. Our study focused both on UTIs occurring near the day of surgery, where the use of prophylactic antibiotics can have an impact, as well as over a longer duration.

Our results show that there was no statistically significant difference in the number of UTIs between the hypospadias group and the control group within 30 days of surgery. Surprisingly, the only boy who incurred a UTI did receive prophylaxis at the time of surgery. When comparing the incidence of UTIs over a longer period, it was significantly higher in the group of hypospadias boys than in the control group. Since no significant difference was found in close relation to the procedure, the use of prophylactic antibiotics in order to lower the rate of UTIs does not appear to be warranted. The frequency of wound infections, which may cause urethroplasty complications during the postoperative course, is an issue that was not the subject of this study.

The higher incidence of UTIs found in the total group makes us consider what the actual causes of these UTIs were. Based on our results, we suggest that the primary operation in itself is not the source of the increased number of infections. Since many complications can occur in association with this procedure, a single urethral reconstruction is not always adequate to restore full function in all hypospadias patients. Therefore, patients often need further surgery and treatment during their childhood; thus inflicting trauma to the urinary tract and promoting the development of scar tissue that may play a role in the boys' vulnerability to a UTI. We suggest that this could

explain the higher frequency of UTIs even several years after the primary surgery. Our data also indicate a higher risk for UTI in the group of hypospadias boys with another urogenital anomaly. This suggests a susceptibility to infection of the urogenital tract that might be inborn.

A limitation regarding the prophylactic antibiotics was that although intended routinely, in about one-third of the operations, it was either missed or not recorded. Therefore, it is uncertain whether the outcome was affected by compliance. However, the only boy who contracted a UTI from birth until 30 days after the surgery did receive prophylactic antibiotics. This raises the question of whether this measure can prevent an infection of the urinary tract. It would have been preferable if prophylactic antibiotics had been given either to all or none of the hypospadias patients. Also, we compared the findings with a control group in which no patients received prophylaxis and, therefore, to make it clearer we could have chosen to exclude the hypospadias patients who did receive antibiotics. However, when we did, there was still no difference in the frequency of UTIs compared with the control group.

Also, some infections might have been missed, because cultures were only taken from patients with typical symptoms of UTIs. This could have been the result of vague symptoms or unawareness by either hospital personnel or patients/parents. Since all patients were not operated on at the same time point, the follow-up time varied from months to years. This difference was found both between the control group and the hypospadias group, as well as within the hypospadias group itself. This limitation is hard to avoid but could have affected the results. One way to improve statistical power could have been to include a greater number of patients, for example on a national level and, therefore, decrease the number of limitations associated with a small study group.

### **Does a change of surgical method affect the complication rate in hypospadias surgery? (Paper III)**

We showed that the change in the hypospadias reconstruction method from the Mathieu procedure to TIP repair in our hands significantly improved the outcome for boys undergoing hypospadias repair. There were no other changes, e.g. modification of surgical method or suture material during the period studied. The operative interventions were performed by the same team of two experienced paediatric surgeons.

Although analysed retrospectively, data were registered prospectively which guarantees the originality and value of our study. The shift in paradigm made it possible to compare the two procedures for hypospadias repair. Thirty-five per cent of all the 142 boys in our series had a complication. This is in accordance with the recent literature

with complication rates ranging from 7–50% (28,30,35,46,57,60-63,71,72). Thus, it is obvious that an effort must be made with the intention to improve the outcome of hypospadias surgery. Paper III is an attempt to do this.

The reason for the change of method of operation from the Mathieu procedure to the TIP repair was the poor results with the Mathieu method before the study started. We also saw an advantage of having fewer basic methods to adapt, since the TIP repair can be used for more variants of hypospadias than the Mathieu procedure. Amongst all the creative procedures described in the literature, we found TIP repair to be the most natural way of handling the developmental shortcomings, to help nature. The technique of TIP repair was not modified during the time period studied and there were no selection criteria, e.g. the quality or measures of the urethral plate, besides the surgeon's preference.

During the first phase there was no difference between the outcomes of the two methods. Insignificant but better results after the TIP reconstruction prompted further and increased use of TIP. The better results with TIP in phase 2 can be attributed to more experience gained by the surgeons. As shown in Table 9 the complications of the Mathieu procedure were reduced from phase 1 to 2 (52% vs. 37%). This difference was not significant ( $p = 0.49$ ).

The duration of follow-up in our series is comparable to that which is reported in the literature. A randomly selected recent retrospective case series (73) reported that the median follow-up was 27 months, range between 6 weeks and 9 years. Most papers did not address the issue of whether the boys were lost to follow-up or excluded from the study. It must be assumed that the follow-up rate is usually 100%, as is the case in our group of boys (29).

The follow-up time is naturally shorter in the second group and one should expect that complications can develop over time. However, in a recent review of the study, 3 years after the conclusion, the results have not changed.

The findings from Paper III are of value when informing parents in preoperative consultations before hypospadias surgery. Furthermore, comparison with other centres is made possible.

### **Meta-analysis comparing the outcome of two methods of distal hypospadias repair (Paper IV)**

This meta-analysis was based on 17 reports that included 1572 patients. The level of evidence ranged from 1b to 2b (38). Fistula was the most common (13%) complication after hypospadias repairs and had a similar rate between the Mathieu procedure and

TIP repair. Both techniques had low rates of postoperative complications, but the risk for urethral stricture was lower after the Mathieu procedure than after TIP repair. Subgroup analysis of the eight RCTs showed consistent results.

To the best of our knowledge, this was the first meta-analysis that showed significant differences in postoperative complications between the Mathieu procedure and TIP technique for hypospadias repair. Like this study, one systematic review (published in 2012) and another meta-analysis (published in 2013) showed that both the Mathieu and TIP repair methods had low rates of postoperative complications (2% to 15%) and overall no significant difference was found between them (27,74). A systematic review of studies published before 2010 concluded that both reconstruction techniques for distal hypospadias had low rates of postoperative complications and did not present a clear consensus on the ideal method (27). However, that study was not included in this present meta-analysis, because of an evidence level of only 4 (38).

Many factors may influence the repair of hypospadias; therefore, comparison and analysis of literature may not be precise. The analysed studies did not always document or report consistently on the presence of a ventral curvature, surgeons' experience, patients' age, previous penile surgery, quality of the penile skin, and configuration of the corpora. Therefore, in this meta-analysis, adjustment for confounding factors was not possible, and we could not take into full account the many variables that are related to fistula formation. Urethral stricture was the second most common complication after hypospadias surgery, with a rate of 2% after the Mathieu procedure and 5% after TIP repair. Our pooled data estimated a higher rate of urethral stricture for TIP repair than for the Mathieu procedure. As with the case for fistulas, possible causes for strictures could not be analysed further because of the lack of information about the confounding factors.

There are several limitations to mention about this study. As stated above, some critical data were only documented rarely, making it impossible to adjust for all possible confounding factors. The significant clinical heterogeneity made our conclusions somewhat conservative, although we used a random effects model. Furthermore, there was a lack of uniform criteria for reporting outcomes and we assumed that the criteria were similar enough to be assessed together. Therefore, future studies with complete data and uniform criteria are needed, in order to identify the best operative intervention for hypospadias. Nevertheless, this study provided valuable and up-to-date information in this field. The level of evidence on which our review was based was high and our conclusion differed from that of some previous reports (27,74). Our results are in favour of the Mathieu procedure over TIP repair, when it comes to lowering the risk of urethral stricture.

## Urinary flow measurements and the prediction of fistulas (Paper V)

The results do not support the hypothesis that it is possible at an early postoperative stage, through urinary measurements findings, to anticipate the development of the complication of a fistula.

There are contradictory reports on the use of urinary flow measurements in the postoperative course of hypospadias repair. Some authors suggest that the quality of micturition should be assessed subjectively and, when possible, confirmed objectively with uroflowmetry (75) without providing any hint about how to interpret or implement the findings. Other authors report that early uroflowmetry appears to be unnecessary, as the voiding history appears to be just as good at alerting the surgeon to the suspicion of urethral stricture after TIP repair. Furthermore, these authors report that there is a spontaneous normalisation, or at least a significant improvement of the urinary flow, in boys after TIP repair, although many boys still had a  $Q_{max}$  in the low normal or obstructive range (76,77).

For the main outcome measure the parameters  $Q_{max}$  (ml/s) and voided volume (ml) were chosen to quickly disclose any abnormality in the urinary flow pattern. These are the most used parameters and easy to collect from a routine urinary flowmetry. The data did not need correction since the age and size of the boys included did not differ significantly between the compared groups. The parameters: Voiding time (s), Time to  $Q_{max}$  (s),  $Q_{average}$  (ml/s) and residual urine (PVR) (ml) were too dependent on individual variations to be of use in this study.

Urinary flow pattern was documented and found to be normally bell shaped in most boys, Table 13. The remaining boys had interrupted/intermittent, slightly flattened or a plateau pattern to their urinary flow that was inconsistent and difficult to interpret. Whether the urinary stream was single and straight, angled or divided was considered unimportant to answer the question being addressed. Mainly as a result of inconsistent individual variations, these excluded parameters may vary by the boy's situation at the flowmetry measurement.

The criteria used to define obstruction on uroflowmetry in the literature are the presence of a plateau pattern and maximum flow ( $Q_{max}$ ) below the 5th percentile on a standard nomogram or two standard deviations (SD) below the mean normal for age (78–86). These parameters are not used consistently throughout the literature. We used the uroflowmetry for comparison between those boys who developed a fistula postoperatively and those who did not, to try to single out any signs of obstruction. Hence, we did not have to set out definitions for the uroflow criteria of obstruction.



As mentioned above, we were not able to prove that through uroflowmetry, it was possible to foresee the development of a fistula. Most boys had already developed a fistula at the time of the urinary flow measurement. In one 5-year-old boy, though, the urinary flow measurements were performed before the fistula appeared. In this boy the Q<sub>max</sub> was 4 ml/s only (compared to the median of 10 ml/s in the other boys) and the voided volume was at the average of 94 ml and the curve was bell shaped. Could this be an indication for further research?

If so, the urinary flow measurement must be performed early postoperatively. Secondly the same method of repair must be used, since there are significant differences between the urinary flow measurement findings related to the different methods of repair as shown in Table 11. Such a study would be possible in boys who had hypospadias repair at the median age of 4 years, as in earlier days at our centre. In the boys of 6 months to 2 years of age now undergoing repair for hypospadias, this would be difficult since the urinary flow measurements are designed for potty-trained boys.

An obstructive urinary flow pattern is often observed in asymptomatic boys following TIP urethroplasty surgery (82). Thus, findings of an obstructive urinary flow pattern could be expected and not the normal bell-shaped urinary flow observed in most of our patients. Olsen et al describes plateau-shaped curves in 31% of boys with hypospadias, whereas all the boys without this malformation displayed normal bell-shaped flow curves (83). These results are supported by our data in Table 13.

It is obvious from Table 13 that the urinary flow measurements are rather unreliable and depend on many factors influencing the boy expected to void in the flowmeter. The volume in the urinary bladder and any type of disturbances could influence the voiding boy and cause bias on the measurements.

### **Strength and limitations and risk of bias in Papers I–V**

All research runs the risk of bias and the research presented in this thesis is no exception.

The strengths of the studies are that the operative interventions were all performed by two paediatric surgeons who cooperated when operating on most of the boys. Therefore, all the boys had undergone standardised hypospadias reconstructive operations by the same team of surgeons. A further strength of this study is that the healthcare in the region is free when needed. Therefore, any drop out or a noncompliance due to socioeconomic effects or factors is unlikely. The urinary flow measurement was performed by the same team of nurses at the out-patients' department. Also, since all laboratory results regarding urine cultures are registered automatically, inadequate charting does not need to be considered as a limitation of

this study. Through our follow-up programme, it will be possible to make a fairer comparison in the years to come. Follow up will be continued due to acknowledged accumulation of complications over time.

The main research limitations are that the studies are a retrospective collection of data albeit in a prospectively gathered database. The studies are also limited by not being randomised. Thus, a bias was introduced in the case selection for the type of repair which was the preference of the surgeon. We cannot exclude the fact that boys with poor urethral plates were considered unsuitable for TIP repair and that the surgeon chose to perform a Mathieu procedure in those cases. Although effort was expended to define the degrees of hypospadias, bias in the interpretations of those degrees must be considered. Underestimations of the degrees due to insidious curvatures might have occurred. The operating surgeons were also responsible for the follow-up, which might have caused a conflict of interest.

Further limitations are the small number of boys included and the short duration of the postoperative follow-up.

There was potential bias in the review process of the literature, including selection bias due to random sequence generation and allocation concealment. Furthermore, performance bias cannot be excluded due to the binding of personnel, and detection bias might be present due to the binding of outcome assessment. Incomplete outcome data (attrition bias), selective reporting (reporting bias), or publication bias was likewise possible.

# Conclusion

The results from Paper I revealed that the complication rate following hypospadias surgery did not correlate with the preoperative symptoms and signs or the degree of hypospadias. Thus, there may be a group of boys with hypospadias without symptoms or signs for whose operations are questionable. The preoperative symptoms and signs should be reported in future reports on the results of hypospadias surgery.

The results from Paper II suggest that patients undergoing primary urethral reconstruction should not receive prophylactic antibiotics in order to decrease the number of UTIs, since we could not find a higher incidence of these infections among hypospadias patients during the initial perioperative period. The results show that boys with hypospadias who have undergone surgery are more prone to incur a UTI compared to a control group. This may be due to damage to the urethra leading to postoperative consequences due to urethral scarring. Thus, this factor is of importance when the boys undergo repeat operative interventions. There are, however, other reasons to administer antibiotic prophylaxis to boys undergoing hypospadias surgery. Minor wound infections leading to wound dehiscence and development of a fistula can occur. Thus, the findings reported here should have an impact on antibiotic administration.

The results reported in Paper III show that the surgical approach matters, at least in our hands. We find it difficult to ignore the clear findings, which support our measures taken for improving the outcome of distal hypospadias repair. As a consequence, the Mathieu procedure was replaced by the TIP repair as the most favoured method for treatment of grade 1–2 hypospadias.

The meta-analysis reported in Paper IV concluded that compared with TIP urethroplasty, the Mathieu procedure for hypospadias reconstruction was associated with a significantly lower risk of postoperative urethral stricture and may be the preferred method for hypospadias repair. The risk of urethrocutaneous fistula was similar. However, the clinical implications of the results can be debated because the risk of stricture in both procedures was low. The implications for research are obvious because there had been no studies that have provided firm guidelines on the best method for the operative intervention for hypospadias.

The results of the study reported in Paper V do not support the hypothesis that it is possible to detect the postoperative complication of fistula after hypospadias surgery. The urinary flow measurement results differed significantly between the three reconstructive methods used at the centre.

# Future aspects

After performing this doctoral project trying to answer some queries, several new considerations have come to mind and are left for further studies.

First the main question if all boys born with hypospadias should undergo surgical repair is still waiting for an answer. I believe the answer is no. For some boys the risk of an intervention simply outweighs the benefits. With regard to addressing the question, the design of such a study could constitute a challenge: should boys with congenital hypospadias be categorised into different groups studied independently depending on their need for surgical interventions? The first groups might comprise boys with an obvious need for surgical interventions, e.g. with meatal stenosis, curvature of the penis or proximal opening of the urethral orifice. Then, those with only a cosmetic problem could have the opportunity to choose if they want to undergo a surgical intervention or not. Finally, the third group with combined surgical and cosmetic problems where surgical intervention may not be urgent, could perhaps wait so that issue could be discussed later with the boy and his guardian when the boy is older.

So, the question remains: do we need a consensus with guidelines providing firm rules for the care of boys affected by hypospadias?

Data in the thesis show that the numbers of UTIs are not distributed evenly and raise the question of whether there is an associated susceptibility among these boys. Determining if some groups of boys, such as those with several malformations, would benefit from antibiotics more than others would be of interest to investigate in a future study.

As pointed out in Paper III the surgical method seems to matter. It is well known that surgeons differ in their choice of operative technique. Therefore, there are numerous reports on successful operative interventions in the hands of surgeons gaining special interest or developing details in the operative interventions suiting their way of thinking and being appropriate in their hands. This leads to reports about successful results of case series. It is a pity that the excellent results cannot be repeated by all other surgeons. Could this situation be solved by guidelines providing the surgeon with directives to handle the great diversity of the hypospadias malformation?

Reading the hypospadias literature there are two main lines of surgical treatment used in hypospadias surgery, i.e. Mathieu perimeatal-based flap (PBF) and TIP. Scrutinising the published case series using these two main approaches it becomes clear that the operating surgeons conduct these two methods in their own way, making minor changes to the main method descriptions. Thus, the reports do not describe the exact same methods of operations, causing bias in any comparative study performed based on these reports. It is critical to provide detailed data and clear definitions to change this shortcoming.

The problem of postoperative urethrocutaneous fistula is a curse for hypospadias surgeons. We would do anything to escape this common problem which occurs in 10–15% of all boys operated on for hypospadias. The question arises whether there are methods enabling us to avoid these fistulas. The solution is still missing. Because the phenotypes of hypospadias are so diverse, the surgeon should be able to improvise. To master this the surgeon needs insight into many different technical approaches. At the same time, and quite contradictory, the surgeon should focus on a few techniques adjusted for the degree of hypospadias, taking into account the individual prerequisites of the patient.

Since we started this project, management of hypospadias has changed quite substantially. With the endeavour to reach full parental consent on the pros and cons of the reconstruction based on our findings, we are now ready to do further patient/guardian-centered research.

How high a complication rate should the surgeon and the patient/guardian tolerate for an operation that primarily addresses an aesthetic issue? How important should we allow genital aesthetics to be? Probably the answer differs between cultural contexts and of course between times, but acknowledging this, bringing up the subject for an open debate would provide us with the tools for tailor-made solutions for the individual patient. Should decisions regarding solely cosmetic intervention be left to the individual boy when he is old enough to make his own decisions?

*Humpty Dumpty went to the fair,  
Humpty Dumpty had a repair;  
All the king's horses, all the king's men  
Couldn't put Humpty together again*

# Populärvetenskaplig sammanfattning

Hypospadi är en missbildning av det manliga urinröret med underutveckling av undersidan av penis. Urinröret mynnar någonstans mellan spetsen på penis och pungen, förhuden är nästan alltid kluven och ibland kröker penis nedåt. Hypospadi kan indelas i olika grader (1–4) utifrån var på penis urinröret mynnar. Ju högre grad, desto större risk att penis också är krökt.

Missbildningen är vanlig och drabbar cirka 1/125 födda pojkar.

Behandlingen av hypospadi är kirurgisk men risken för komplikationer är stor. Utmaningen har sporrat många genom historien att utveckla nya eller förädla äldre tekniker, men man tvistar fortfarande om vilken teknik som är den bästa.

Hypospadi opereras ofta i blöjåldern, 6–18 månader, med tanken att barnet inte ska ha något minne av ingreppet.

Beslutet om operation fattas av vårdnadshavarna i samråd med kirurgen. Symtom som dåligt urinflöde och/eller en krökning av penis saknas ofta och operationen genomförs av kosmetiska skäl. Detta väcker frågor om etik och kring rätten att bestämma om det mest privata. Barnet är ju inte delaktigt i processen. För att underlätta för föräldrarna att bedöma riskerna och ge möjlighet till ett mer välgrundat beslut inför en eventuell operation har vi inspirerats till kartläggning av såväl inneboende patientspecifika förutsättningar samt till inventering av de olika kirurgiska metodernas resultat.

Syftet med den första studien var att bedöma om komplikationerna efter kirurgi kunde kopplas till hypospadigrad, operationsteknik samt till om pojkarna hade några symtom innan operationen. I studien beskrivs fyra olika operationstekniker.

En kohort bestående av alla pojkar som opererades primärt för hypospadi mellan januari 2011 och april 2014 inkluderades i studien.

Vi kunde se att komplikationsrisken var hög och att den inte korrelerade till hypospadigrad eller symtom innan operation och kanske finns det en grupp pojkar där operation kan ifrågasättas.

Andra studien gjordes för att utvärdera om risken för urinvägsinfektion hos pojkar opererade för hypospadi före, i samband med eller efter operation berättigar

användande av antibiotikaprofylax. Denna studie gjordes som en fall-kontroll studie där kontrollgruppen bestod av friska pojkar som opererades för ljumskbräck vid samma operationsavdelning.

Pojkar med hypospadi och i synnerhet de med andra medfödda missbildningar i urin- eller könsorganen, utvecklade oftare urinvägsinfektioner med symtom. Infektionerna uppstod dock inte före eller i samband med operationerna. Därför kunde vi inte hävda att förebyggande antibiotika behövdes för att undvika urinvägsinfektion efter hypospadikirurgi.

Den tredje studien gjordes för att analysera om ett byte av kirurgisk teknik skulle påverka komplikationsrisken. Vi mätte här endast de komplikationer som krävde ytterligare en sövning för att åtgärda. Vi fann att dessa komplikationer minskade sedan vi successivt ersatt Mathieus teknik med TIP för de distala (grad 1–2) hypospadierna.

I den fjärde studien gjordes en metaanalys av komplikationsfrekvensen mellan de två vanligaste operationsmetoderna för distal hypospadi: Mathieu och TIP avseende de två vanligaste operationskrävande komplikationerna uretrokutan fistel respektive uretrastriktur. Risken att utveckla en fistel var lika stor med de bägge metoderna, men strikturerna var signifikant vanligare efter TIP.

Med vår femte studie (accepterad för publicering i *Journal of Pediatric Urology*) undersöker vi kopplingen mellan dåligt urinflöde och uppkomst av fistel mellan urinrör och hud efter rekonstruktion för hypospadi. Urinflödesmätning gjordes på pott-tränade pojkar minst 4 veckor efter operationen. Tre olika tekniker jämfördes. Vi kunde inte bevisa att det gick att förutse eller förklara uppkomsten av fistlar, men vi kunde se att urinflödet var bättre efter Mathieu.

Tillsammans utgör de fem studierna underlag för att bättre förstå risker och vinster inför ett beslut om kirurgisk åtgärd i avsaknad av symtom. Risken för komplikation som innebär ytterligare en operation och sövning är stor vid denna typ av kirurgi och tycks inte påverkas av symtom, graden av hypospadi och inte heller av vilken operationsteknik kirurgen väljer.



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