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Hypospadias

Factors Associated with Origin and Successful Treatment of this Anomaly

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ACADEMIC DISSERTATION
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ABBREVIATIONS

AR	androgen receptor
CI	confidence interval
DES	diethylstilbestrol
DHT	dihydrotestosterone
HCG	human chorionic gonadotropin
HFGS	Hand-foot-genital syndrome
IUGR	intrauterine growth retardation
MAGPI	meatal advancement and glanuloplasty
OR	odds ratio
SD	standard deviation
SPD	synpolydactyly
TDS	testicular dysgenesis syndrome

ABSTRACT

In hypospadias, one of the most common congenital anomalies in boys, the urethral meatus is located on the ventral aspect of the penis or even on the perineum. It is caused by incomplete closure of the tissue on the undersurface of the penis. The etiology of hypospadias is probably multifactorial, involving genetic and environmental factors. The treatment is surgery, the aim being a penis with normal appearance and function.

The aim of this study was to assess the effects of hypospadias and its surgical correction on the life of the patient as an adult. It was also sought to establish the occurrence of this anomaly.

In the clinical part of our series the study population comprised of 64 patients operated for hypopadias at Tampere University Hospital between 1963 and 1976. In a study comparing the sexuality of hypospadias patients to that of patients operated on the genitals, 64 patients circumcised for phimosis were selected as age-matched controls. The patient records of hypospadias patients were analyzed retrospectively and a questionnaire was mailed to them in 1994. All patients treated for hypospadias before nine years of age among boys born 1970-1986 were identified from the Finnish National Hospital Discharge Registry for a study of temporal trends and geographical variation in the prevalence of hypospadias in Finland. In a study of pregnancy-related risk factors of hypospadias, all 490 boys born with hypospadias in Finland between 1996 and 2001 were selected from the Finnish Birth Defects Registry and 1470 age-matched male controls from the Finnish Medical Birth Registry. Information on pregnancy-related factors was

obtained from the Medical Birth Registry.

Significant differences were noted between hypospadias and phimosis patients in erectile and urinary function, as well as in satisfaction with penile appearance and surgical result. Problems in voiding and erection and especially poor cosmetic result were associated with dissatisfaction with the outcome. Many patients would have preferred a longer follow-up after surgery. The mean prevalence of hypospadias among boys born 1970-1986 was much higher than had previously been reported, 28.1 per 10,000 male live births. It remained constant throughout the study period. Nonetheless, there was substantial geographical variation in the prevalence of operated hypospadias. Birth weight, young maternal age and presence of some anomaly other than hypospadias were risk factors for the condition.

A great proportion of the previously reported differences between hypospadias patients and other men arise from surgery on the male genitalia and the out-of-the-ordinary appearance it causes. Even patients with a less than perfect technical result are able to live a satisfactory sexual life. An operation with good short-term results and few complications satisfies the patient also as an adult. The overall appearance as perceived by the patient is the most important factor in producing a good result. The previously reported low prevalence of hypospadias was due to underreporting of cases to the Finnish Malformation Registry. The geographical variation in the prevalence of operated hypospadias has many possible explanations, although none of them were verified by methods we used. Studies on the relationship between poor intrauterine growth and hypospadias are clearly called for. A nutritional factor might provide a mode of intervention for the prevention of this disorder.

1. INTRODUCTION

In hypospadias, the urethral meatus is located on the proximal and ventral aspect of the glans or shaft of the penis or even on the perineum. The foreskin may be incomplete ventrally and abundant dorsally and there may be ventral penile curvature. Hypospadias is thought to be caused by incomplete closure of the tissue on the undersurface of the penis. The reasons for this are unclear. The etiology of the condition is probably multifactorial, involving genetic and environmental factors. The most consistently reported risk factor for hypospadias is low birth weight (for example, Carmichael et al. 2003).

Hypospadias is one of the most common congenital anomalies in males, with a widely quoted incidence of 1 in 300 male live births. In fact, the birth prevalence of hypospadias varies widely across different populations, ranging from 0.37 to 41 per 10,000 infants (Källen et al. 1986). The reported prevalence increased rapidly before the mid-1990s in many countries (Jensen et al. 1995, Anonymous 1995, Paulozzi et al. 1997).

The aim of primary hypospadias surgery is to achieve a functionally and esthetically normal penis (Manzoni et al. 2004). There is a paucity of long-term, patient-reported data on the outcome and effects of hypospadias surgery, particularly as regards sexual function (Nelson et al. 2005). It would however appear that hypospadias or surgery for it does not prevent satisfactory and complete sexual life (Mureau et al. 1995).

The aim of this present study was to establish the occurrence and etiology of hypospadias, the effect of the anomaly and surgery for it on the sexual life of the patient, and factors associated with patient's opinion on the surgical result.

2. REVIEW OF THE LITERATURE

2.1. Normal urethral development

The development of the male external genitalia is a complex process which is currently incompletely understood, especially as regards the formation of the glandular urethra (van der Werff et al. 2000). The mature urethra has a pseudostratified and stratified columnar epithelium in the penile portion and a nonkeratinizing, stratified squamous epithelium in the glandular portion. The former is of endodermal, the latter of ectodermal origin.

In the third week of development, the first sign of external genitals, a pair of elevations called cloacal folds appear (Sadler 2004). These folds unite cranially to form a genital tubercle (the future penis), while caudally they are subdivided anteriorly into urethral folds (the future urethra) and posteriorly into anal folds.

During the first six weeks of gestation it is impossible to distinguish between male and female sex (Sadler 2004). Thereafter, the genital tubercle (now called the phallus) elongates under the influence of testosterone. This elongation pulls the urethral folds forward to form the lateral walls of the urethral groove.

It is fairly safe to say that the urethra forms when the genital folds fuse, although even this has been disputed (van der Werff et al. 2000). This takes place between 8 and 14 weeks of gestation under the influence of testosterone secreted by the fetal testes (Sadler 2004, Kurzrock and Karpman 2004).

The process involved in the development of the glandular urethra has caused most controversy. In a mechanism commonly presented in embryology textbooks, ectodermal cells penetrate into the glans from its tip forming an epithelial cord (Glenister 1958, Sadler 2004). This occurs during the fourth gestational month and later this cord obtains a lumen.

According to recent studies by van der Werff and associates (2000), the formation of the glandular urethra begins very early during embryogenesis, when both swellings of the genital tubercle fuse and their surface epithelium adheres together. An epithelial plate of a double layer of ectoderm is formed. This plate is disconnected from the surface ectoderm by programmed cell death. Luminization of the epithelial plate takes place secondarily by apoptosis.

The theory of endodermal differentiation suggests that the glandular urethra develops via differentiation of the endodermal urogenital sinus (Kurzrock et al. 1999).

All theories explain the anatomy of the mature urethra: different kinds of epithelium in the penile and glandular portion. The hypothesis presented by van der Werff and associates (2000) explains the formation of the urethra by the same basic morphological processes (luminization, fusion and definitive differentiation) as are used to describe the formation of other structures.

The prepuce forms when the double layer of epithelium of ectodermal origin, with

the mesoderm between these layers, encircles the whole glans (van der Werff et al. 2000). This process begins when or at least is not complete until the genital folds have fused completely (Baskin 2000, van der Werff et al. 2000). This explains the fact that in hypospadias the prepuce is absent in ventral surface of the penis and excessive dorsally .

2.2. Classification of hypospadias

The most common and oldest classification of hypospadias is based on the preoperative meatal position of the meatus (Browne 1936). These are from distal to proximal: glanular, distal penile, proximal penile, penoscrotal junction and perineal. A more useful approach is based on the meatal position after correction of the ventral curvature: cases are divided into anterior (glanular and subcoronal), middle (distal penile, midshaft, proximal penile) and posterior (penoscrotal, scrotal, perineal) (Barcat 1973, Duckett 1992).

Distal hypospadias are most common, comprising at least 50-75 % of all cases, while middle and proximal hypospadias are markedly more uncommon (Barcat 1973, Calzolari et al. 1986, Duckett 1992).

2.3. Occurrence of hypospadias

Hypospadias is commonly cited as one of the most common congenital malformations, with an estimated prevalence of about 1 in 300 male live births (e.g., Retik and Borer 2002). However, the birth prevalence of hypospadias varies widely

across different populations (Källen et al. 1986). Variation has been reported both between different countries and within countries. Birth prevalences of hypospadias as given in various reports are presented in table 1.

Author, Year	**Incidence**	**Area**
Porter et al. (2005)	5.0/1,000 male births	California, USA
Boisen et al. (2005)	46/1,000 births	Copenhagen, Denmark
Ahmed et al. (2004)	4.6/1,000 births	Scotland
Aschim et al. (2004a)	2.47/1,000 male live births	Norway
Kurahashi et al. (2004)	3.9/10,000 births	Hokkaido, Japan
Carmichael et al. (2003)	3.3/1,000 male births	California, USA
Dolk et al. (2004)	0.4 - 2.4/1,000 births	Various areas in Europe
Pierik et al. (2002)	7.3/1,000 male births	Rotterdam, the Netherlands
Virtanen et al. (2001)	3/1,000 male births	Turku area, Finland
Chambers and Malone (1999)	3.2/1,000 births 1.9/1,000 births	Southampton, England Portsmouth, England
Leung et al. (1985)	4.44/1,000 male births	British Columbia, Canada
Avellan (1975)	1.39/1,000 births	Sweden
Sweet et al. (1974)	8.2/1,000 male births	Rochester, Minnesota, USA

Table 1. The birth prevalence of hypospadias in various areas and countries.

In the mid-1990s an increasing incidence of male genitourinary anomalies was reported, including hypospadias, cryptorchidism and testicular cancer, as well as declining semen quality in several industrialized countries was reported (Jensen et al. 1995, Anonymous 1995). A study based on two birth defect surveillance systems indicated a doubling in the rate of hypospadias in the United States during the 1970s and 1980s, from approximately 20 to almost 40 cases per 10,000 births (Paulozzi et al. 1997). During the same period, the reported birth prevalence of hypospadias in Denmark and Norway had increased from approximately 7 to 15-20 per 10,000 births. The reported prevalence in Finland had increased slightly, but remained below that in other Nordic countries (approximately five per 10,000 births), until the beginning of the 1990s, when it started to increase rapidly, reaching 28 per 10,000 male births in 1997 (National Research and Development Centre for Welfare and Health, Finland 1974-1997, Ministry of Environment and Energy, Denmark 1995).

2.4. Etiology and pathogenesis of hypospadias

The etiology of hypospadias is multifactorial, with involvement of genetic and environmental factors. Fusion of the urethral folds in the seventh to twelfth week after ovulation, leading to the fully formed penis, is dependent of testosterone produced by the fetal testis and its conversion to dihydrotestosterone (DHT) (Aaronson et al. 1997). Any factor which disrupts this mechanism can cause hypospadias.

2.4.1. Genetic factors

Genetic factors have been proved to play a role in the development of hypospadias in only a very small subset of patients. Defects in testosterone biosynthesis, androgen receptor, 5α-reductase genes or in their levels in the preputium are considered to be very uncommon and if there are defects, they exist mostly in rare, more severe hypospadias (Gearhart et al. 1988, Hiort et al. 1994, Allera et al. 1995, Bentvelsen et al. 1995, Sutherland et al. 1996, Aaronson et al. 1997, Albers et al. 1997, Holmes et al. 2004). Despite this, several quite recent studies indicate that AR gene mutations are common in certain types of hypospadias (Lim et al. 2000, Aschim et al. 2004b). A decreased testosterone response to HCG stimulation has been proposed as a possible mechanism for hypospadias but seems to be rare (Feyaerts et al. 2002). Another proposed mechanism is a defect in some cellular signal mechanism other than testosterone and DHT. Examples of this might be a defect in or failure of normal expression in the homeobox genes, transcriptional regulators directing embryonic development (Donnenfeld et al. 1992, Podlasek et al. 1997). There are rare cases of autosomal dominant inheritance of hypospadias as part of the Hand-foot-genital Syndrome (HFGS) (Frisen et al. 2003). There is, further, a dominantly inherited condition, synpolydactyly (SPD), with at least one report of affected males also having hypospadias (Goodman et al. 1997). In both of these conditions there is a defect in the HOX-genes: HOXA13 in HFGS and HOXD13 in SPD.

Bauer and colleagues (1981) analyzed the family history of 307 boys with hypospadias. In 21 % of cases some other relative had hypospadias, in 14 % this relative was a brother and in 7 % the father. If father and son both have hypospadias

the risk of another boy having hypospadias is 26 %. Familial clustering has been perceived to implicate a genetic and heritable component (Baskin 2004). A number of studies show a strong heritability component in the development of hypospadias (Stoll et al. 1990, Fredell et al. 2002a). Based on the findings of Fredell and associates (2002a), it seems fairly safe to suggest that monogenic factors cause hypospadias in a small proportion of affected families, but that there is a multifactorial cause for the majority of cases. The genetic predisposition could moreover cause hypospadias in combination with certain environmental factors (Fritz and Czeizel 1996).

2.4.2. Environmental factors

The most consistently reported risk factor for hypospadias is low birth weight (Chen and Woolley 1971, Calzolari et al. 1986, Fredell et al. 1998, Akre et al. 1999, Weidner et al. 1999, Gatti et al. 2001, Fredell et al. 2002b, Hussain et al. 2002, Carmichael et al. 2003). There is also an inverse correlation between hypospadias and parity, i.e. the condition is more common in the first pregnancy (Akre et al. 1999, Hussain et al. 2002, Carmichael et al. 2003). Advancing maternal age is thought to be a risk factor for hypospadias, although this conception has been challenged by at least one investigator (Harris 1990). Early age at menarche increases the risk of hypospadias in the offspring (Calzolari et al. 1986, Fisch et al. 2001, Carmichael et al. 2003, Porter et al. 2005). Other pregnancy-related risk factors suggested to increase the risk are maternal vegetarian diet, short gestation, low weight of the placenta, severe pre-eclampsia and threatened abortion (Calzolari et al. 1986, Stoll et al. 1990, Akre et al. 1999, North and Golding 2000).

Up to 1975 threatened abortion was treated with diethystilbestrol (DES), and an increasing risk of hypospadias has been suggested in the offspring of women exposed to DES in utero (Klip et al. 2002). More recently, the magnitude of this transgenerational effect has been questioned (Brouwers et al. 2005, Palmer et al. 2005). Maternal exposure to progestins has also been linked with hypospadias (Aarskog 1979, Calzolari et al. 1986), the connection being however questioned in a meta-analysis by Raman-Wilms and associates (1995).

Men under 20 years of age are at increased risk of fathering boys with hypospadias (McIntosh et al. 1995). Other suggested paternal risk factors are abnormalities in the scrotum or testis and low spematozoa motility and abnormal sperm morphology (Sweet et al. 1974, Fritz and Czeizel 1996).

Risk factors for hypospadias ascertained in case-control studies are presented in Table 2. Only case-control studies are presented, as these give the most reliable information on risk factors at the individual level.

Reports suggesting an increasing incidence of hypospadias and other male genitourinary anomalies such as cryptorchidism and testicular cancer as well as declining semen quality in several industrialized countries, received considerable publicity in the 1990s (Carlsen et al. 1992, Jensen et al. 1995, Anonymous 1995). Since these changes had occurred over a relatively short period of time, environmental rather than genetic factors were thought to provide a plausible explanation (Givercman et al. 1993). First environmental estrogen-like compounds were blamed (the so-called estrogen hypothesis) (Sharpe and Skakkebæk 1993) but

later the view was expanded to include environmental antiandrogens as endocrine disrupters (Toppari et al. 1996). Since there are temporal and geographical associations between these abnormalities, as well as frequent combinations of more than one abnormality in one individual, the existence of a pathogenetic link has been suggested (Skakkebaek et al. 2001). The reason for these male reproductive problems has been suggested to be a maldeveloped testis caused by environmental factors aided by genetic susceptibility. The theory envisaging poor semen quality, testis cancer, undescended testis and hypospadias as symptoms of one underlying entity was named the testicular dysgenesis syndrome (TDS).

Author (year)	**Risk factor**	**OR (95% CI)**
Källen (1988)	Weak contractions	3.0 (1.3-6.8)
	Cesarean section	2.0 (1.0-4.0)
	Artificial induction of delivery	4.1 (2.0-8.3)
McIntosh et al. (1995)	Paternal age <20	2.0 (1.1-3.7)
	Paternal age 20-24	1.3 (1.0-1.7)
	Paternal age 45-49	1.9 (1.0-3.9)
Weidner et al. (1999)	Birth weight 2,499 g or less	3.4 (2.8-4.1)
	Birth weight 2,500-2,999 g	1.8 (1.5-2.1)
	Birth weight 3,000-3,499 g	1.3 (1.1-1.4)
	Previous stillbirth	2.0 (1.3-3.3)
North and Golding (2000)	Maternal vegetarian diet	4.9 (2.1-11.9)
	Influenza (first 3 months)	3.2 (1.5-6.8)
Källen (2002)	Primiparity	1.3 (1.2-1.4)
	Low maternal education	1.2 (1.1-1.3)
Pierik et al. (2004)	Low maternal education	2.0 (1.1-3.9)
	SGA	4.2 (1.2-14.7)
	Turkish origin of mother	3.0 (1.2-7.7)
	Mother's poor health	3.6 (1.6-8.1)
	Father smoking	3.8 (1.8-8.2)
Porter et al. (2005)	Maternal age (vs <20) 25-29 y	1.2 (1.0-1.4)
	Maternal age 30-34	1.4 (1.2-1.7)
	Maternal age 35-39	1.5 (1.3-1.9)
	Maternal age >40	1.7 (1.2-2.5)
	Diabetes mellitus	2.2 (1.0-4.6)

Table 2. Risk factors for hypospadias based on case-control studies.

2.5. Treatment of hypospadias

The only means of treating hypospadias is surgery, the objective being to achieve a functionally and esthetically normal penis (Manzoni et al. 2004). This requires a straight penis with normal-caliber urethra and slit-like meatus at the tip of the naturally reconfigurated glans. The patient should be able to void standing without straining, spraying or pain (Mouriquand and Mure 2004).

The ideal time to correct primary hypospadias is when the patient is 6 to 12 months old. The penis is big enough (Schonfeld and Beebe 1942) but genital awareness has not begun (Lepore 1979, American Academy of Pediatrics 1996). A further but less ideal opportunity is when the patient is three to four years old, by which time he is mature enough to collaborate with treatment.

2.5.1. Surgical techniques

There are three main steps in the surgical treatment of hypospadias: correction of the ventral curvature, creation of the missing part of the urethra and reconstruction of the ventral radius of the penis (Mouriquand and Mure 2004). The preoperative meatal position alone imposes serious limitations when one plans an operation to correct hypospadias. The development of the foreskin, the configuration of the glans and groove, penile size, the presence or absence of penile curvature and scrotal variations all have a role in defining the severity of hypospadias and the appropriate operative technique. No one technique is totally satisfactory: hence over 200 techniques have been described for the correction of hypospadias (Baka-Jakubiak 1998).

The first step in an operation for hypospadias is correction of the ventral curvature, which is usually caused by tethering of the ventral hypoplastic skin. Degloving the penis straightens it in 80 % of cases. If this does not suffice, the urethral plate is usually freed from the corpora. In those 5 % of cases where the curvature remains after these procedures, the cause is usually asymmetric corpora cavernosa (Mouriquand and Mure 2004). Correction requires a dorsal corporoplasty.

In most cases the urethral plate can and should be preserved as it forms the basis for replacement of the missing urethra. Most of the methods used are not new. If the urethral plate is wide and healthy, it can be tubularized around an 8 fr catheter (Thiersch-Duplay technique). If it is too narrow for this, it can be incised longitudinally and then tubularized (Snodgrass technique). Alternatively, a rectangle of pedicled preputial mucosa (onlay urethroplasty) or a flap of ventral penile skin (Mathieu technique) can be laid on it (Mouriquand and Mure 2004). If the length of the missing urethra is less than two centimeters and the distal urethra is not hypoplastic, adequate coverage can be achieved by mobilizing the whole penile urethra. If the urethral plate cannot be preserved, the missing urethra is replaced by making a tube from preputial or buccal mucosa. In hypospadias cripples the techniques are similar to those in primary operations. In complex cases, several approaches may have to be combined but the techniques are the same as above, in principle.

The last stage in the surgery is the reconstruction of the ventral radius of the penis. This is achieved by meatoplasty and glanuloplasty, creating a mucosal collar around

the glans, covering the neourethra and covering the ventral surface with skin from the dorsal surface. When needed, the prepuce can be reconstructed in order to obtain a normal appearance instead of the circumcised-looking penis that is most common after operation for hypospadias (Frey and Cohen 1989, Klijn et al 2000, Erdenetsetseg and Dewan 2003).

Although the norm in most cases is single-stage repair, two-stage procedures have their place especially in severe cases or in repeat surgery (Bracka 1995, Mouriquand and Mure 2004). An old technique in which the penis is straightened by removing the urethral plate and ventrally grafted with preputial or buccal mucosa in a first step and tubularized a few weeks later in second stage has been revived in the 1990s.

Most of the currently favoured techniques are decades old, while some once very popular newer techniques have given disappointing results (Mouriquand and Mure 2004). Examples are MAGPI, Devine-Horton and bladder graft urethroplasty. Many new methods and modifications of old techniques are presented every year. It would seem that the frequently mentioned number of over 200 operative techniques for correction for hypospadias is even an understatement.

The three operations (Denis Browne, Mathieu and Ombredanne) used among patients in clinical studies are presented in Table 3 (Browne 1936, Borer and Retik 1999, Androutsos 2003). All these procedures follow the above-mentioned principles of hypospadias repair: straightening of the penis followed by reconstruction of the urethra over the urethral plate and, at the end of the procedure, reconstruction of the anterior surface of glans and penis to cover the neourethra.

	Ombredanne	Denis Browne	Mathieu
Staged	Yes/No	Yes	No
Terminal meatus	Yes	No	Yes
Origin of neourethra	Ventral skin proximal to meatus	Ventral skin distal to meatus	Ventral skin proximal to meatus
Reconstruction of ventral side	Preputial and ventral skin	Ventral skin	Dorsal penile skin

Table 3. Comparison of the three operative methods for correction of hypospadias used among patients in this study.

2.5.2. Short-term results

The most common complication of surgery for hypospadias is a poor cosmetic result (Mouriquand and Mure 2004). This is usually due to irregular and asymmetric scarring with excess skin. Urethral fistula is the second most common complication. Meatal stenosis is also quite common. Other complications include urethral strictures, urethrocele and balanitis xerotica obliterans. There are also reported complications which have made some operations less common: urethral prolapse (associated with use of bladder mucosa in correction), urethral stones (use of hairy skin), sticking meatus (use of bladder mucosa) and meatal retraction (MAGPI operation) (Hastie et al. 1989, Kinkead et al. 1994, Mouriquand and Mure 2004).

The Mathieu procedure gives excellent results; meatal stenosis occurs in 1 % and fistulae in 5 % of patients (Minevich et al. 1999). The half-moon shaped meatus is a common source of criticism. The urethral mobilization technique (Koff) carries a

very low fistula rate but meatal stenosis is common (20 % of cases) (Mouriquand and Mure 2004). The onlay procedure has a complication rate of 15-50 % (Elbakry 1999). Methods which involve an incised urethral plate give poor results in proximal cases while results in distal cases are good (Decter and Franzoni 1999, Snodgrass and Lorenzo 2002, Elicevik et al. 2004). Buccal graft urethroplasties have a high rate of reoperations and complications, even over 50 % (Duckett et al. 1995, Metro et al. 2001).

2.6. Follow-up and consequences of hypospadias in adulthood

There is paucity of long-term, patient-reported data on results and effects of hypospadias surgery (Nelson et al. 2005). This is particularly true in the case of sexual function; even decades must pass before the adult outcome after surgery becomes apparent. Many patients are lost to follow-up and sexuality can be a difficult area to discuss even among those who are available for follow-up.

It has been suggested that surgery on the genitals is exceptionally harmful on the patients'psychological development (Purschke and Standke 1993). Children who have undergone surgery on the uro-genital organs suffer more psychiatric disorders than children who have been operated on the nose, ears or throat (Blotcky and Grossman 1978).

2.6.1. Growth and development

Boys with hypospadias achieve normal height, weight, testicular and pubertal

development (Avellan 1976, Bracka 1989) and their serum testosterone is also normal (Bracka 1989). Only those who have had an operation for severe, i.e. posterior hypospadias, often manifest deficiencies in the levels of testosterone, luteinizing hormone and follicle stimulating hormone as adults (Eberle et al. 1993). These patients commonly have other developmental abnormalities such as micropenis, small testicles, unpalpable prostate and gynecomastia.

2.6.2. Appearance of the operated penis

Bracka (1989) noted that 44 % of 213 patients operated for hypospadias were dissatisfied with the status of their penis (Bracka 1989). Most considered the cosmesis to be as important as function. Almost half of patients operated for posterior hypospadias are dissatisfied with the cosmetic result (Eberle et al. 1993). In a population with varying degrees of hypospadias, 25 % of patients were dissatisfied with the appearance of their penis, over twice the frequency among controls (Mureau et al.1995). Twice as many patients (84.7 %) as controls (40 %) considered their penile appearance to be different from that of other men, the most common reason for this being the circumcised appearance. Despite this, the main reason for dissatisfaction with appearance was penile size. Over one third of the patients and one out of five controls considered their flaccid penis to be too small.

2.6.3. Voiding

Spraying of the urinary stream is common among patients opearted for hypospadias (Berg et al. 1981, Bracka 1989). Maximum urinary flow may be decreased among

patients operated for hypospadias, more commonly in patients with proximal hypospadias (Svensson and Berg 1983, Eberle et al. 1993). This usually indicates an asymptomatic stricture in the neourethra (Garibay et al. 1995), and this being a common complication of hypospadias surgery, uroflowmetry should be utilized on each attendance in the follow-up of operated patients until after puberty (Malyon et al. 1997).

2.6.4. Sexual and social behaviour and function

Hypospadias patients have their first sexual intercourse somewhat later in life than other men (Svensson et al. 1981, Berg et al. 1981, Berg and Berg 1983, Bracka 1989, Mureau et al. 1995). The severity of hypospadias correlates with several aspects of sexual life (Bracka 1989, Mureau et al. 1995). Patients with a more proximal anomaly have their sexual debut later and they are more inhibited in seeking sexual contacts.

The quality of operative surgery seems to play a role: when the meatus is at the tip of the glans, the first intercourse occurs at an earlier age than when the meatus is located on ventral side of the penis (Bracka 1989). Patients' opinion of the appearance of the penis has a similar effect: if a patient considers his penis to be normal-looking he has his first sexual intercourse at an earlier age and has more partners.

Hypospadias patients have been reported to have fewer partners than controls and they are more seldom married (Berg et al. 1981, Svensson et al. 1981). They are

claimed to be less secure of their sexual identity and to have poorer ability to form emotional, sexual or social relationships (Svensson et al. 1981, Mureau et al. 1995).

Despite the above-mentioned differences between hypospadias patients and other men, hypospadias or surgery for it does not preclude a satisfactory and complete sexual life (Mureau et al. 1995).

Most patients are able to have satisfactory sexual intercourse (Bracka 1989, Mureau et al.1995). Bracka (1989) reported that a third of patients have a dribbling ejaculation and in 4 % ejaculation is absent. In a study of 19 patients with severe perineoscrotal hypospadias, only seven had satifactory ejaculation (Miller and Grant 1997). According to those studies which have reported ejaculation problems, they are markedly rarer among unselected hypospadias patients (Kenawi 1975, Berg et al. 1981). There are no solid data available on the fertility of men born with hypospadias (Mieusset and Soulie 2005).

2.6.5. Hypospadias in adults

The normal location of the urethral meatus is relative. In a study of 500 middle-aged men, only 55 % had the urethral meatus in the distal third of the glans, a place considered to be normal (Fichtner et al. 1995). Moreover, 13 % had anterior hypospadias. Neither 10 patients out of 16 with coronal or subcoronal hypospadias, nor their partners were unaware of any abnormality.

As stated above, the norm in hypospadias surgery is to correct this defect in

childhood, but it is not uncommon for a urologist to meet an older patient with uncorrected hypospadias. Also, a young or middle-aged patient with relative hypospadias, the urethral meatus being located somewhat ventrally, is not a rarity. In developing countries, hypospadias may be left untreated until adulthood (Senkul et al. 2002). If an adult or adolescent patient is to be treated the techniques are similar to those employes in pediatric cases but complications occur more frequently (Hensle et al. 2001, Senkul et al. 2002).

3. AIMS OF THE STUDY

The aim of this presents series was to study the effects of hypospadias and surgery for it on the life of the patient as an adult. Further, we sought to elucidate the epidemiology and etiology of this anomaly. More specifically, the objectives were:

1. to establish if reported problems in sexual life in hypospadiac patients are due to surgery for this anomaly spesifically or due to surgery on the genitals generally (I).

2. to ascertain whether patients operated for other genital problems complain of similar problems to hypospadiacs in micturition and sex life (I).

3. to establish whether better short-term results of corrective operations correlate positively with patients' satisfaction with their sexual life and voiding ability as adults (II).

4. to identify the kind of problems which are associated with dissatisfaction with the result of corrective surgery for hypospadias (II).

5. to assess the temporal trends in the prevalence of hypospadias in Finland (III).

6. to study determinants of the geographical variation in the prevalence of hypospadias in Finland (IV).

7. to assess the role of pregnancy-related factors in the etiology of hypospadias (V).

4. STUDY POPULATION AND METHODS

4.1. Sexual and social life of men operated for hypospadias in childhood and adult satisfaction with the result of surgery (papers I and II)

In the clinical part of our study (papers I and II) the study population consisted of 64 patients operated for hypopadias at Tampere University Hospital between 1963 and 1976. Patient records were analyzed retrospectively. Hypospadias were classified, operations were defined and complications recorded. Thirty-three of the hypospadias were classified as anterior, 11 middle and 20 posterior. Twenty patients had been operated by the Mathieu technique, whereas the Denis Browne technique had been used on 35 patients. The Ombredanne procedure had been the method in six cases and other, unclassified techniques in three.

In a study comparing the sexuality of hypospadias patients to that in patients operated on the genitals (paper I), 64 patients circumcised for phimosis were selected as age-matched controls operated at the same hospital during the same year as each of the hypospadias patients. A detailed questionnaire form was mailed to all 128 patients in November 1994, with a covering letter explaining the purpose of the study: to evaluate long-term results of penis operations performed in childhood. The form contained 27 questions for hypospadias patients and 26 for controls. The same questionnaire was sent once more to patients who did not respond the first time. The mean ages of hypospadias and control patients at the operation and at the time they received the questionnaire were 3.6 vs. 4.2 years and 29.5 vs. 29.9 years, respectively. There was no significant difference between the two groups in the

occupational class of parents and in the age of mothers.

The same data were used in a study examining the factors which lead to (dis)satisfaction with the result of hypospadias surgery (paper II). Three patients were excluded from the study because the exact method of corrective surgery for hypospadias could not be defined.

The data were analyzed using Student's t-test and the chi-square test. Probabilities <0.05 (2-tailed) were considered statistically significant.

4.2. Temporal trends and geographical variation in the prevalence of hypospadias in Finland (papers III and IV)

All patients treated for hypospadias (ICD-8 codes 752,20-752,22 and 752,29 and ICD-9 code 7526B) before nine years of age among boys born 1970-1986 were identified from the Finnish National Hospital Discharge Registry. Patients' place of birth and the number of male live births were identified from the National Birth Registry. Place of birth was obtained for each patient based on mother's place of residence at the time of the birth. To achieve full coverage of all operated cases, an upper age limit as high as nine years was selected. Each patient could be identified by a unique personal ID number. Duplicate records were eliminated, as well as patients not born in Finland.

The cumulative prevalence from birth to eight years of age overall for each birth cohort and for each of the 355 municipalities in Finland was calculated by dividing

the cumulative number of operated patients by the number of male live births in the index year. Demographic data including distance to the nearest city, proportion of adult population in the highest and lowest social class, as well as the proportion of the population employed in industry or forestry and farming in each municipality were obtained from Statistics Finland based on census 1970.

The temporal trend and association of the explanatory factors with the prevalence of hypospadias was assessed using Poisson regression methods. In paper IV, municipalities were grouped into five categories (university hospital districts) and smaller categories (provinces) to obtain classes with both reasonable size and meaningful contrast in the studied exposure variable. For each category the overall prevalence was calculated using the numbers of cases and male live births, and the population-weighted category-specific mean value of the explanatory variable was assigned. The category with the largest population was selected as reference.

4.3. Pregnancy-related factors in the etiology of hypospadias (paper V)

All male children born with hypospadias between 1996 and 2001 in Finland were selected from the Finnish Birth Defects Registry. Three male controls for each case were selected from the Finnish Medical Birth Registry, with matching year of birth. The validity of hypospadias diagnoses was ascertained from medical records if there was any doubt about the correct diagnosis or if the degree of hypospadias was not evident.

The source population comprised of 176,845 boys born during the study period; 490

hypospadias patients and 1470 controls were selected. One case was excluded as the sex of this patient had been changed to female. Five controls were excluded from the data: two stillborns and three controls with diagnoses of chorda penis, epispadias and hypospadias. The final number of subjects in the analyses was 489 cases and 1465 controls.

Information on pregnancy-related factors was obtained from the Medical Birth Registry established in 1987 and maintained by the Finnish National Research and Development Centre for Welfare and Health. It is based on obligatory notifications from hospitals either electronically or on paper. Completeness is checked annually using vital statistics from Central Population Registry and Statistics Finland. The Medical Birth Register contains information on characteristics of the mother (e.g. reproductive history and socio-economic background) and child (birth weight, height and Apgar score) as well as pregnancy and delivery (diagnoses, procedures, mode of delivery).

Conditional logistic regression was used to estimate the odds ratio for the statistical analysis. The criterion was presence of hypospadias. Confidence intervals were estimated using likelihood methods. Stratification factors (year of birth) were used as covariates in the analysis.

5. RESULTS

5.1. Sexual and social life of men operated for hypospadias in childhood (paper I)

Forty-six (71.9 %) hypospadiacs and 43 controls (67.2 %) returned the questionnaire. The mean age of the hypospadiacs at the time of operation and at the time they filled in the questionnaire were similar to those of controls: 3.6 vs. 4.2 years and 29.5 vs. 29.9 years, respectively. The percentages of different operations in those who responded were fairly similar to those of the operations in the whole material (Denis Browne 51.2 % and 50 %, Mathieu 34.9 % and 28.6 %, Ombredanne 7 % and 8.6 %, respectively).

There was no difference between hypospadiacs and controls in education, socio-economic status and in military rank. Hypospadiacs were married or lived in marriage-like relationships slightly less often than controls and had fewer children than controls (average 0.8 vs 1.1). Hypospadiacs had had their first sexual intercourse six months later than controls and had had fewer intercourses during the preceding four weeks. All above-mentioned differences were however statistically non-significant. There was no difference between the groups in opinions regarding the quality of their sex life or penile size. Significant differences were noted in erectile and urinary function, as well as in satisfaction with the penile appearance and surgical result (Table 4).

	Hypospadias patients	Circumcised patients	Significance
Erectile problems	21.7 % (10/46)	7.0 % (3/43)	p=0.054
Ejaculation problems	13.0 % (6/46)	_	p<0.05
Dissatisfied/appearance	21.7 % (10/46)	2.3 % (1/43)	p<0.01
Voiding problems	80.4 % (37/46)	46.5 %(20/43)	p<0.001
Dissatisfied/result	32.6 % (15/46)	4.7 %(2/43)	p<0.01

Table 4. Differences between hypospadias patients and circumcised patients in areas related to hypospadias and surgery for it.

All six patients with ejaculation problems had been operated by the Denis Browne technique. Four of these cases had been penoscrotal, two had been midpenile. There was no statistically significant difference between the groups in satisfaction with the size of the penis. The most common voiding problems were spraying, wrong direction and after-dripping. In addition to being dissatisfied with the surgical result, 11 out of 15 hypospadias patients would have liked to have a reoperation, as against only one circumcised patient. All 11 had problems with urination, four also with ejaculation. Active follow-up after surgery had been discontinued on average at the age of 7.1 years; 40 % of hypospadiacs would have liked a longer follow-up, most often until the late teens (15-18 years old). Thirty per cent of controls would have preferred a longer follow-up. There were no significant differences in attitude towards health care or physicians, 8 out of 10 hypospadias patients and almost 9 out of 10 controls expressing at least fairly positive attitude towards health care, whileattitudes toward physicians were even better.

5.2. Adult satisfaction with the result of surgery for hypospadias (paper II)

Forty-six patients (71.9 %) returned the questionnaire and 43 were included in the final statistical analysis. Three of the patients were not included because the exact operative technique could not be verified. The mean age and duration of follow-up for patients included in the study were 29.7 (range 20.5-38.6) and 27.0 (19-31) years, respectively. Among those who responded 51.2 % of hypospadias were anterior, 16.3 % middle and 32.6 % posterior, while among all operated hypospadiacs the corresponding percentages were 51.6, 17.2 and 31.2 %. Operative techniques and late complications in all 61 hypospadiacs and in those 43 who returned the questionnaire were also fairly similar. Thus, those who returned the questionnaire well represent all hypospadiacs operated in our hospital. Patients operated by the Denis Browne technique had had complications more often than others, the most common problems being fistulas (9 cases), meatal stenosis (5), persistent curvature (4) and urethral diverticulum (3), whereas in those operated using the Mathieu technique the only 2 complications were persistent curvatures.

Twenty-seven of the 43 patients (62.8 %) who returned the questionnaire expressed satisfaction with the result of the operation, while 14 expressed dissatisfaction. Satisfied patients had fewer problems in voiding and erection than those who were not satisfied, and were also markedly more often satisfied with the appearance of their penis and their sexual life. The most important differences between satisfied and dissatisfied patients are presented in Table 5.

	Satisfied (n=27)	Dissatisfied (n=14)	Significance
Complication after the operation	22.2 % (6/27)	57.1 % (8/14)	$p<0.05$
Complication (Denis Browne)	(4/11)	(8/12)	-
Voiding problems	65.4 %	100 %	$p<0.05$
Erection problems	7.7 %	28.6 %	-
Dissatisfaction with appearance	0.0 %	46.2 %	$p<0.01$
Dissatisfaction with sex life	11.5 %	50 %	$p<0.05$

Table 5. Prominent differences between patients satisfied and dissatisfied with the result of corrective surgery for hypospadias

Satisfied patients were married or lived in marriage-like relationship more often than those dissatisfied (70.4 % vs. 50.0 %) and had sexual intercourse more often (mean 6.2 vs. 4.4 times in the preceding four weeks). In contrast, they had fewer children (mean 0.76 vs. 1.00) and were older at the time of their first sexual intercourse (mean 16.7 vs. 15.6 years). These differences are, however, not statistically significant.

Patients operated using the Mathieu and Ombredanne techniques were more often satisfied than those operated by the Denis Browne technique. Patients operated by the Mathieu technique also had fewer voiding problems than those operated by the Denis Browne technique. However, there was no difference between the Denis

Browne and Mathieu groups in satisfaction with the appearance of the penis, 19 % of patients being dissatisfied with it in both groups.

The most common voiding problems were spraying, wrong direction of urinary stream and after-dripping. Problems in sexual function comprised too short duration of erection, persistent curvature and pain during erection.

Fifteen patients (34.9 %) would have preferred a longer follow-up. Their follow-up had in fact lasted slightly longer than in those who were satisfied with the duration of the follow-up (7.6 vs. 7.2 years of age). Those operated by the Denis Browne technique had been followed up longer than patients operated by other techniques, until they were 8.7 years as against 6.8 (Ombredanne) and 5.2 (Mathieu). Despite this, 40.0 % of them would have wanted the follow-up to last longer compared to 33.3 % in the Ombredanne and 37.5 % in the Mathieu group. Those who would have preferred a longer follow-up were markedly less often satisfied with the result (35.7 % vs. 87.5 %, $p<0.05$), and more often dissatisfied with the appearance of their penis (35.7 % vs. 4.4 %, $p<0.05$), and had more problems in voiding (100.0 % vs. 62.5 %, $p<0.05$). These sources of dissatisfaction were not caused by complications, as these patients had had fewer complications after surgery.

5.3. Temporal trends in the prevalence of hypospadias in Finland (paper III)

A total of 549,176 male children were born alive in Finland between 1970 and 1986, approximately 30,000 annually. The total number of patients treated for hypospadias in that period was 1,543. The mean cumulative prevalence of hypospadias requiring treatment by the age of eight was 28.1 per 10,000 male live

births (95 per cent confidence interval 26.7 - 29.5). In the regression analysis of cumulative prevalence by birth year, more heterogeneity was observed between individual years than could be expected on the basis of chance alone ($p<0.05$). However, there was no evidence for a linear trend across birth years. The prevalence remained constant throughout the study period (relative change 0.00 per year, 95 per cent confidence interval -0.01 to +0.01). Based on the upper 95% confidence interval, a relative increase of 12% or greater over the 16-year study period could be excluded. Dividing the study period into five-year periods did not improve the fit ($p>0.5$), nor did a sinusoidal function of birth year ($p>0.5$). The figure for the prevalence of hypospadias in Finland between 1970 and 1986 compared to the incidence officially reported by the Finnish Malformation Registry can be seen in the original publication.

5.4. Geographical variation in the prevalence of hypospadias in Finland (paper IV)

In a comparison between geographical areas, there was substantial variation in the prevalence of operated hypospadias between provinces, from 21.4 per 10,000 male births to 31.9. The province with the highest prevalence was Kymi, the reference province was Uusimaa (31.53/10,000 male live births). Provinces with significantly lower prevalences were Turku and Pori (25.08), Mikkeli (21.39), Karjala (21.81), Kuopio (23.99) and Vaasa (20.36). Division of the country into five university hospital districts also revealed wide variation in the prevalence of hypospadias (Figure 1). No significant differences were observed between the eastern and western parts of the country. On the south-north axis, the prevalence of hypospadias

was significantly lower in the second most southernly fifth of the country compared to the southernmost area.

In analysis of socio-demographic factors an association emerged between the prevalence of hypospadias and remoteness (distance from closest city). The highest rate was observed for suburban areas (1 - 10 km to the nearest city) and the lowest for remote areas situated at distances less than 100 kms from the nearest city. There were no differences in the prevalence of hypospadias between areas with different levels of education, social class or proportion of employees working in industry or farming and forestry. There was no significant difference in the prevalence of hypospadias between municipalities grouped by the mean age of mothers.

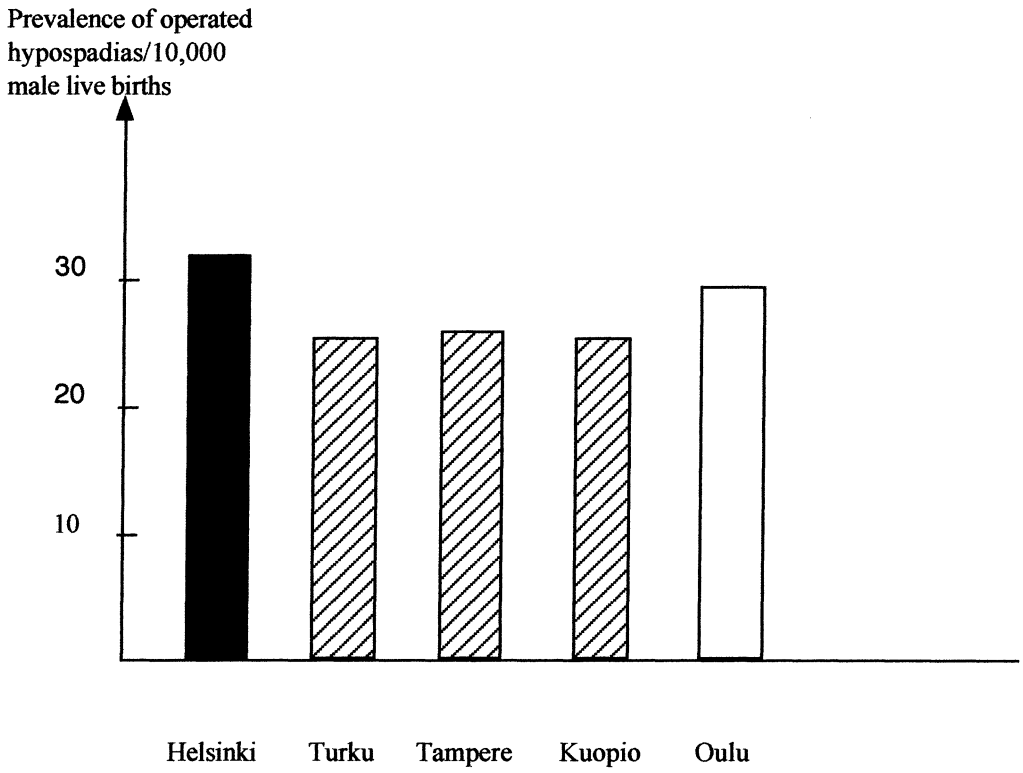

Figure 1. The prevalence of operated hypospadias in Finland grouped by university hospital district. In shaded areas the 95 % confidence interval differs significantly from reference (black).

5.5. Pregnancy-related factors in the etiology of hypospadias (paper V)

In univariate analysis, maternal factors associated with an increased risk of hypospadias were young age of the mother and nulliparity. Characteristics of the child associated with hypospadias included small size at birth, low Apgar score and other congenital anomaly. In vitro-fertilization and other assisted reproduction techniques were associated with a non-significantly increased risk.

The mean age of mothers among the cases was 28.6 years (SD 5.5), compared to 29.8 years (SD 5.3) in the control group. Mothers whose offspring had hypospadias had had fewer pregnancies and childbirths than the mothers of the control children. There was no significant association between maternal smoking during pregnancy and hypospadias; 11.3 % of cases and 12.6 % of controls had smoked through pregnancy, one % of cases and controls had quit smoking during the first trimester. The risk of hypospadias was inversely correlated with birth weight and height. The mean weights and heights of cases and controls were 3,192 (SD 843) grams vs. 3,528 (SD 650) grams and 48.9 (SD 4.1) cm vs. 50.3 (SD 2.9) cm, respectively. Multiple birth was associated with a higher risk of hypospadias than in single birth. The one minute Apgar score was inversely correlated with the risk of hypospadias. Children with 6 to 8 Apgar points had an OR of 1.5 compared to boys with Apgar scores 9 or 10 (95% CI 1.2-2.0). With Apgar scores below 6, the OR was 2.5 (95% CI 1.5-4.2). Other congenital anomalies were strongly associated with hypospadias, i.e. hypospadias was more common in children with multiple anomalies.

In multivariate analysis, only birth weight (OR 0.9993 per gram with 95% CI

0.9992 - 0.9995), maternal age (OR 0.957 per year with 95% CI 0.936 - 0.979) and presence of an anomaly other than hypospadias (OR 5.07 with 95% CI 3.21 - 8.00) remained statistically significantly associated with hypospadias (Table 6). Being small for gestational age increased the risk significantly (OR 2.96 with 95% CI 1.49-5.86). The risk of hypospadias decreased with increasing maternal age. If a child had some urinary tract anomaly other than hypospadias, the risk of hypospadias was five-fold compared to children who had no anomalies (OR 5.00, 95% CI 2.88-8.70). Malformations of other organs also increased the risk (OR 3.64, 95% CI 2.49-5.32).

One-hundred and twenty of the hypospadias cases (24.5 %) were classified as major. When minor hypospadias were not included in the statistical analysis, the risk factors remained the same. The presence of some other anomaly increased the risk of hypospadias (OR 14.05 , 95% CI 4.65-42.51). Birth weight and age of mother were inversely correlated with the risk of hypospadias (OR 0.9993 with 95% CI 0.9989-0.9998 and OR 0.93 with 95% CI 0.88-0.98, respectively).

Factor	Odds ratio (95% CI)
Birth weight (g)	
<2,500	1.69 (1.06 - 2.72)
2,500 - 2,999	1.73 (1.21 - 2.48)
3,000 - 3,499	1.07 (0.82 - 1.40)
>3,499	Reference
Maternal age (years)	
<20	1.52 (0.78 - 2.96)
20 - 24	0.99 (0.71 - 1.37)
25 - 29	Reference
30 - 34	0.58 (0.44 - 0.78)
>34	0.60 (0.42 - 0.84)

Table 6. The effect of birth weight and maternal age on the risk of hypospadias, based on multivariate analysis.

6. DISCUSSION

Only a handful of case-control studies on sexuality or patient satisfaction among hypospadias patients as adults had been published before our series (Berg et al. 1981, Svensson et al. 1981, Berg and Berg 1983, Mureau et al. 1995). Since then, others have published descriptive long-term studies on these topics (Lam et al. 2005, Nelson et al. 2005, Nuininga et al. 2005, Liu et al. 2006) but only one group has had control patients, as we had (Bubanj et al. 2004).

6.1. Sexual and social life of men operated for hypospadias in childhood

It has been reported that hypospadiacs are sexually less active, that their sexual debut is delayed and that they have less qualified professions than controls (Berg et al. 1981). They may also be more inhibited in seeking sexual contact and have a more negative appraisal of their genital organs (Mureau et al. 1995, Mondaini et al. 2002). In the first part of our series, we studied whether these differences could be caused by surgery on the genitals in general. Circumcised patients were selected as controls, as circumcision is not routinely done in Finland, only when there is a clear medical indication for surgery. Circumcision causes an unusual but not unpleasant appearance of the penis. Usually, surgery for hypospadias leaves a similar circumcised-like appearance.

We suggest that a great proportion of previously reported differences is attributable to surgery on the male genitalia and the out-of-the-ordinary appearance it causes, although none of the controls expressed dissatisfaction with the appearance of the

penis. The psychological characteristics of hypospadias patients may not be as different as previously thought. The authors of the study on psychosexual adjustment of hypospadias patients most frequently referred to highlight the importance of circumcised appearance as a source of negative perception of the penis (Mureau et al. 1995). They suggest that patients should be informed that also after circumcision of a normal penis, the prepuce is lacking and the glans is exposed.

In our study, the quality of hypospadias patients' sex life did not differ from that among control patients. In general, most recent studies of sexual life among patients operated for hypospadias have given results similar to ours (Mureau et al. 1995, Nelson et al. 2005) with only one exception (Bubanj et al. 2004). In addition, in the study by Mondaini and associates (2002) hypospadias patients had more difficulties in initiating contact with the opposite sex compared to other men, but the rate was much higher among nonoperated patients (67 vs. 14 %). It has to be noted that the studies in question have been undertaken in different cultural environments, and attitudes toward penile appearance may vary.

There was a statistically significant difference in the frequency of problems in voiding between hypospadias and control patients. This was to be expected, as the Denis Browne operation does not give a terminal meatus, which is almost prerequisite if urinary dysfunction is to be avoided (Bracka 1989). The fact that so many control patients complained of spraying and after-dripping was surprising, suggesting that all complaints of voiding problems among patients operated for hypospadias may not be attributable to surgery. In this study the frequency of voiding problems among hypospadiacs was 80 % compared to 45 % among controls.

This frequency of voiding problems much exceeds those given in most reports of long-term outcome. A possible explanation here is that patients may have reported even minor, occasional problems. In addition, one explanation for voiding problems in circumcised patients is that the indication for surgery had been medical, for example balanitis, which could have caused meatal stenosis.

The attitudes of hypospadias patients towards the health care system and physicians were slightly less positive than those of controls. This may result from dissatisfaction with their treatment, as one out of every three hypospadiacs was dissatisfied with the result. They would also have wanted the active follow-up to last longer, until the teens. This had previously been suggested by Bracka (1989) and Mureau and colleagues (1995), and since our studies it has also been recommended by others (Nuininga et al. 2005). It has been shown that additional complications can present even 14 years after surgery (Nuininga et al. 2005).

Our results confirm that even patients with a less than perfect technical result are able to live a satisfactory sexual life. Sexual life and success in life in general among hypospadiacs did not differ from those of circumcised patients. However, hypospadiacs had more voiding disturbances, which emphasizes the need to continuously develop better surgical methods and the need for longer follow-up.

6.2. Adult satisfaction with the result of surgery for hypospadias

In the second part of our study we sought to establish the factors underlying dissatisfaction with the result of surgery. The frequency of chronic complications

(12.5 % in Mathieu- and 50.0 % in Denis Browne-type operations) is similar to that shown by others (Kelalis et al. 1977, Rickwood and Anderson 1991). The much higher incidence of complications in patients operated by the 2-stage Denis Browne technique was expected and offers further proof that the methods currently used yield superior results.

When the long-term result of surgery is to be evaluated, the best judge is the patient himself. There are significant differences between physician reported and patient-reported outcomes of hypospadias surgery (Mureau et al. 1996). In the present series, two thirds of the 43 patients were satisfied with the result. There was a clear difference in complication frequency between satisfied and dissatisfied patients, suggesting a correlation between short-term and long-term results. The same trend was also found among patients operated only by the Denis Browne technique, which usually gives inadequate results by current standards and which was used for more proximal cases. Patients who had suffered more complications during treatment were more dissatisfied with their current status. This would indicate that an operation with good short-term results and few complications also satisfies the patient as an adult. The same result has been reported by Liu and associates (2006).

Patients operated by the Denis Browne technique were more often dissatisfied with the result of the surgery compared to the other methods. This can be understood in the light of the observed connection between fewer complications and better long-term results and the fact that patients operated by the Denis Browne technique had more late postoperative complications than patients operated by other techniques.

Even though most patients complained of voiding problems, there would seem to be no strong correlation between voiding abnormalities and patients' overall satisfaction with the result. It would appear that the overall appearance as perceived by the patient and patients' satisfaction with their sexual function are more important in producing a good result. Almost every satisfied patient was also satisfied with the appearance of the penis, whereas almost half of the dissatisfied patients were dissatisfied with it. The importance of appearance as a component of satisfaction has also been reported by Bracka (1989).

Dissatisfaction with the result may also cause dissatisfaction with sex life. On the other hand, those with problems in their sexual life may blame hypospadias for them. It is interesting that three of the dissatisfied patients complained of inadequate duration of erection, which is unlikely to be due to the hypospadias or its repair. Although satisfied patients were married or lived in marriage-like relationship more often and had sexual intercourse more often, they had fewer children and had had their first sexual intercourse later than dissatisfied patients. This might indicate that overall dissatisfaction does not hamper sexual relationships.

Adequate duration of follow-up is also difficult to assess. Although patients who would have preferred a longer follow-up were more dissatisfied with the result, lengthening of follow-up would probably not change the result, but might nevertheless give them the feeling that everything had been done as well as possible. A longer follow-up has been argued for as giving patient and doctor a chance to discuss possible cosmetic or functional improvements (Mureau et al. 1995).

6.3. Strengths and weaknesses of the clinical studies

Our clinical studies have strengths which are not easily attained even in centres with much a larger patient base. Over two-thirds of the operated patients participated, which constitutes much better coverage than the majority of recent studies; no study has reported better coverage (Mureau et al. 1995, Bubanj et al. 2004, Lam et al. 2005, Nelson et al. 2005, Nuininga et al. 2005, Liu et al. 2006). Although the number of patients was small, only one of the above-mentioned studies had more. The participating patients well represented all operated patients. The need for control patients was emphasized in a recent editorial in the Journal of Urology by one of the most acclaimed urologists in the field of "hypospadiology" (Snodgrass, 2005).

There were also weaknesses in our studies. They lacked validated instruments to measure sexual function and outcome of surgery. The first, and so far the only, attempt to create an objective method of evaluating the esthetic results of hypospadias surgery was introduced in 2001 (Holland et al., 2001). The number of patients was small and the surgical methods employed were partially outdated. This is common in long-term studies on surgery for hypospadias (Nelson et al. 2005, Snodgrass 2005). Short-term results with large numbers of patients are widely available. These facts induced us to direct our further studies to the occurrence of hypospadias.

6.4. The prevalence of hypospadias in Finland between 1970 and 1986

The first of the epidemiological studies in this project was undertaken because several reports had proposed a very low prevalence of hypospadias in Finland with a slight increase during the 1970s and in 80s, and a sudden increase thereafter (for example, the Danish Ministry of Environment and Energy 1995, the Finnish Malformation Registry data). According to our results, the prevalence of hypospadias in Finland remained constant in the birth cohorts from 1970 to 1986. In addition, our results showed a substantially higher overall prevalence than previously reported

Our findings suggest that the previously reported low prevalence was due to underreporting of hypospadias cases to the Finnish Malformation Registry. Substantial underreporting of hypospadias and other malformations to these registries has previously been demonstrated in Finland and other Nordic countries (Källen et al. 1986, Hemminki et al. 1993).

We calculated the prevalence of hypospadias indirectly, using Hospital Discharge Registry data. All children are examined by a pediatrician at birth. After the neonatal period, under the national child health surveillance system all children are examined by a physician four times during the first two years of life and then annually up to the age of six years. Attendance is almost 100 per cent (Hermansson et al. 1994). All patients with an abnormality are referred to a specialist center for evaluation and treatment, in this case surgery. A prospective cohort study from Denmark has shown that the true prevalence of hypospadias increased four-fold

from 1.03 % at birth to 4.64 % at three years, as physiological phimosis dissolves and detection of this anomaly becomes easier (Boisen et al. 2005).

It seems likely that our study design allowed us to estimate the prevalence of hypospadias and especially temporal trends fairly precisely. With great probability it takes account of almost every hypospadias severe enough to warrant treatment. The true prevalence of hypospadias is likely to be even higher, as minor forms of it may stillescape notice or be left untreated. The diagnostic criteria for hypospadias have not been completely defined and both overdiagnosis and underreporting of this abnormality may occur, as the limit between normal variation and very distal hypospadias is vague. In a study of 500 "normal adult" men , only 55 % had a normal meatus in the distal third of the glans penis, while 13 % had anterior hypospadias and 32 % had a meatal location between these (Fichtner et al. 1995).

The possibility that the prevalence of unoperated cases would have increased could not be assessed from the hospital discharge registry, as no information was available on outpatient visits. Changes in treatment policy in that direction are improbable. From 1996 on the prevalence of hypospadias ascertained by the Finnish Birth Defects Registry has been approximately 28 per 10,000 male births, which is very similar to our findings. A prospective study on live-born boys born in Turku from 1997 to 1999 showed that 0.3% of them had hypospadias, also consistent with our figures (Virtanen et al. 2001).

Since the publication of our results, studies on the prevalence of hypospadias using a method similar to ours have been made in Japan (Kurahashi et al. 2004). Our study

has been mentioned as one of first two to have validated malformation registry data.

In a European malformation registry data validation study, it was concluded that current evidence does not support the conception of an increasing trend in the incidence of hypospadias (Dolk et al. 2004). It was suggested that access to surgical or hospital discharge records is essential for comprehensive case ascertainment. Further, the relatively late age at surgery in some cases and countries causes delay in surveillance. It was also suggested that varying sensitivity to diagnose, report and correct this anomaly, may bias temporal and international comparisons. While our study design has its flaws, it would appear to be close to optimal in the current setting.

6.5. Regional differences in the prevalence of hypospadias in Finland

In the second epidemiological study, we analysed the prevalence of hypospadias in relation to place of birth in Finland and found a substantial variation which was only partly explained by the explanatory factors we used. The variation was smaller than in other countries with programs for registering hypospadias (Källen et al. 1986).

Our study method was similar to that described in paper III assessing the prevalence of hypospadias in Finland and temporal changes in it. It has similar strengths and weaknesses but also additional methodological limitations.

Comparability of case ascertainment and reporting is critical when registry-based data are used in evaluating geographical differences in the prevalence of hypospadias

(Toppari et al. 2001, Virtanen et al. 2001). Variation in reporting and ascertainment may partly explain the observed differences in the prevalence of operated cases in different parts of Finland. This has also been held to be a contributing factor elsewhere (Paulozzi 1999). Even minor differences in the criteria for the diagnosis of hypospadias and treatment of it may cause marked differences when long time trends or numerous cases are analysed. Differences between areas in the number of pediatric surgeons may also be a factor. University hospital districts with the largest pediatric surgery resources may be more ready also to operate less severe cases.

The authors of a large international study on the epidemiology of hypospadias explain the wide variation within and between countries by levels of ascertainment, genetic factors and possible modifying factors (Källen et al. 1986). All these factors may account for the differences observed in the prevalence of operated hypospadias also in Finland.

There is wide variation in living environments in Finland. While the southern and western parts of the country are relatively densely populated and industrialized, the eastern and northern parts include large sparsely inhabited areas. Agricultural occupations are more common in the western and central parts of the country. Thus, environmental differences cannot be ruled out as a reason for the regional differences in the prevalence of hypospadias.

We found lower prevalence rates of hypospadias in remote areas than in cities. This could be attributable to either environmental or behavioural factors. Many compounds and their derivatives in industrial and agricultural use contain substances

exerting estrogenic effects which could influence the development of the genital organs (Sharpe and Skakkebaek 1993, Katzenellenbogen 1995, Anonymous 1995, Barthold et al. 1999).

Because fetal exposure to environmental estrogens has been associated with reported increases in the prevalence of hypospadias, children of women occupationally exposed to estrogenic compounds may run an increased risk. A high rate of cryptorchidism has been reported among sons of female gardeners, and pesticide use has been associated with a high orchidopexy rate (Garcia-Rodriguez et al. 1996, Sloth Weidner et al. 1998). An increased risk of hypospadias has been reported among sons born on Norwegian farms where pesticides and tractor spraying equipment had been used (Kristensen et al. 1997). Employment in either industry or agriculture was not strongly related to the prevalence of hypospadias in our study. It is conceivable that this negative finding is due to the fact that occupational information was available only at group level (proportion of population employed in different occupations). Also, only a small proportion of persons in a given occupation are exposed to any specific agent. Thus, only a very strong environmental agent could have caused changes detectable by the method used in this study. A better means of assessing individual risk factors would be a case-control study, whereas an ecological study like this is the best method for detecting temporal and regional differences.

A recent study based on Y chromosome haplotype variation showed that there are significant differences between eastern and western Finland in the two Y chromosome haplotypes (Kittles et al. 1998). Thus, it is possible that genetic

differences may explain some of the geographical variation in the prevalence of hypospadias in Finland.

We were not able to identify major risk factors for hypospadias based on a large nationwide ecological study. In the last part of our study we therefore sought to clarify the etiology of hypospadias at individual level.

6.6. Pregnancy-related factors in the etiology of hypospadias (paper V)

Judging from our results, birth weight, maternal age and presence of an anomaly other than hypospadias constitute the most important risk factors for hypospadias. Every new malformation in Finland is reported to the Finnish Birth Defects Registry (FRCM) by the birth hospital. Unfortunately our method allowed us to study the effect of only a limited number of possible risk factors. Detailed information on intrauterine growth and placenta, for example, are not collected in routine perinatal registries and are therefore missing.

Our results confirm the importance of low birth weight as a risk factor for hypospadias. This has been the only consistently reported risk factor for hypospadias in previous studies (Fredell et al. 1998, Weidner et al. 1999, Gatti et al. 2001, Hussain et al. 2002). We found a linear relationship between birth weight and risk of hypospadias. Other indicators of fetal size, e.g. height, were not associated with hypospadias in multivariate analysis. Further, twinning or Apgar score were no longer significant risk factors after adjustment for birth weight, suggesting that their effect is explained by fetal growth. Intrauterine growth retardation is probably of

early gestational cause, which coincides with the development of the genital organs (Hussain et al. 2002). The main risk factor for intrauterine growth retardation (IUGR) is thought to be placental insufficiency, which has also been proposed as a risk factor associated with hypospadias (Akre et al. 1999, Gatti et al. 2001). In animal studies, poor maternal nutrition before and throughout pregnancy restricts fetal growth in part by altering placental structure (Kind et al. 2004).

There is some evidence that micronutrient supplementation of undernourished mothers may increase the birth weight of their offspring (Fall et al. 2003). Vitamin C and E supplementation may reduce the risk of pre-eclampsia, which has been associated with hypospadias (Calzolari et al. 1986, Akre et al. 1999). A maternal vegetarian diet has been proposed to be a risk factor for hypospadias, and vegetarians have been shown to be at higher risk of a deficiency of vitamins B-12 and D, despite dietary supplements (North et al. 2000, Larsson and Johansson 2002). In their study reporting an association between hypospadias and vegetarian diet, North and associates (2000) proposed three mechanisms in the vegetarian diet which could explain this association: phytoestrogens in soy products, artificial chemicals and deficiency of essential nutrients. We were not in a position to assess mothers' nutrition, but further research on nutrition and hypospadias is clearly justified.

Besides low birth weight, we found a strong inverse correlation between maternal age and hypospadias. The effect was linear, without any indication for a threshold. The effect of parity disappeared after adjustment for mother's age. The finding on maternal age is in contrast to some previous results. Earlier reports indicate that older mothers have an increased risk of giving birth to a boy with hypospadias

(Fisch et al. 2001, Carmichael et al. 2003, Porter et al. 2005). The effect of increasing maternal age has been most evident for severe cases (Fisch et al. 2001). However, several studies have shown no effect or a negative (albeit statistically nonsignificant) correlation (Chen and Woolley 1971, Hussain et al. 2002, Pierik et al. 2004). In a Swedish nationwide case-control study, a statistically non-significantly increased risk of hypospadias in offspring was found both among young (19 years or less) and old (40 years or above) mothers (Akre et al. 1999). Two of the studies showing an increased risk with advancing maternal age were based on a Californian registry which has recently included only severe cases (Carmichael et al. 2003, Fisch et al. 2001). The ratio of minor to major hypospadias has traditionally been considered to be 3 to 1, exactly equal to the ratio in our data (Paulozzi et al. 1997). As stated above, many additional minor hypospadias may appear as phimosis dissolves during the first three years of life (Boisen et al. 2005). Thus, studies using registries covering only major cases may have a selection bias. Nevertheless, a large case-control study from Washington State in the United States indicated that increasing maternal age is a risk factor for hypospadias in the offspring (Porter et al. 2005). We have no explanation for the difference between that study and our results, although the reported incidence of hypospadias is much higher in that study population compared to ours.

We noted an association between hypospadias and other congenital anomalies, which is consistent with findings elsewhere (Chen and Woolley 1971). Genetic disorders are commonly associated with multiple congenital anomalies, including hypospadias. This is also consistent with the suggested testicular dysgenesis syndrome, proposed as an explanation for male genital disorders (Skakkebaek et al. 2001). However, it

was difficult here to disentangle the role of hereditary factors from environmental influence affecting the risk of several abnormalities.

After adjustment for other factors, assisted reproduction was not associated with an increased risk of hypospadias. This finding is consistent withthat in a recent study on clomifene use and hypospadias (Sorensen et al. 2005).

Our results bring out the need for studies on the relationship between poor intrauterine growth and hypospadias. Some nutritional factor might provide an intervention for prevention of this disorder, comparable to the use of dexamethasone to prevent adrenogenital syndrome (Silver 2000). The association between risk of hypospadias and maternal age calls for further elucidation.

7. CONCLUSIONS

1. A great proportion of previously reported differences in the sexual life of hypospadias patients is attributable to surgery on the male genitalia and especially the out-of-the-ordinary appearance it causes. Even patients with a less than perfect technical result are able to live a satisfactory sexual life.

2. Sexual life and success in life in general among hypospadiacs do not differ from those among circumcised patients. However, hypospadias patients here had more voiding disturbances.

3. An operation with good short-term results and few complications also satisfies the patient as an adult.

4. The overall appearance as perceived by the patient and patients' satisfaction with their sexual function are vital in producing a good long-term result.

5. The prevalence of hypospadias in Finland remained constant in birth cohorts from 1970 to 1986. Our results showed a substantially higher overall prevalence than previously reported. The previously reported low prevalence was due to underreporting of cases to the Finnish Malformation Registry.

6. There was a substantial variation in the prevalence of hypospadias in relation to place of birth in Finland which was only partly captured by the exposure indices we used. The variation is smaller than that within other countries with programs for

registering hypospadias.

7. Low birth weight, young maternal age and presence of some anomaly other than hypospadias are risk factors for hypospadias.

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10. ORIGINAL PUBLICATIONS