Long-term clinical outcomes after reconstructive surgery in adults born with bladder exstrophy

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Abstract:

Introduction

The classic bladder extrophy (extrophia vesica) is one of the rare congenital anomalies that falls under the spectrum of the extrophy-epispadias complex (EEC) along with cloacal extrophy and epispadias. The pathogenesis is not completely understood but most theories are based on a midline defect. The classical bladder extrophy is the most common of all three and boys are more frequently affected. The literature shows the effects of bladder extrophy reconstructive surgery on the long-term clinical outcomes of the patients. This study examines the long-term clinical outcomes in the patients followed at the UMCG.

Objectives

The aim of this study is to evaluate renal function in the patients, to determine whether they frequently suffer from urinary tract infections and if they are dry or suffer from urinary incontinence. Besides this, the metabolic effects (i.e. pH and vitamin B12 levels) as well as stone formation risk following bladder augmentations will be analysed.

Material and methods

Sixty-one adult patients born with bladder extrophy were identified at the department of urology at the UMCG. Forty-eight patients were included in the study; 13 were excluded for various reasons. All the data were retrospectively retrieved from the medical files of patients.

Results

The median age of the patients was 36 years. Of the 48 included patients, 56% were women and 44% were men. Sixty-nine percent of the patients were dry either by spontaneous voiding or by continent urine deviation, while 31% were incontinent (incontinent stoma, completely incontinent). Eighty-three percent of patients had a normal renal function. Thirty-one patients had suffered a urinary tract infection at least once in the last five years, while nine patients had experienced more than 3 urinary tract infections in the past three years. Sixteen patients (33%) developed stones; 13 had an augmented bladder. Only one patient with an augmented bladder was vitamin B12 deficient.

Conclusion

Bladder extrophy does not have a negative influence on the renal function, nor on stone formation and vitamin B12 levels in the long term. There is no significant correlation between acidosis and bladder augmentation. This study population reported a higher number of urinary tract infections than occurs in the Dutch population with no preference for either gender. Finally, the majority of patients are dry and do not suffer from urinary incontinence.
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Introduction

Background

The EEC-complex

The classical bladder exstrophy (extrophia vesica) is one of the rare congenital anomalies that falls under the spectrum of the exstrophy-epispadias complex (EEC), which is a serious form of malformation of the abdominal midline. This spectrum includes defects of the urinary system, reproductive system, gastro-intestinal system and musculoskeletal system (1-3). The complex can be divided into three groups: epispadias, classic bladder exstrophy and cloacal exstrophy (3).

The most common type is the classical bladder exstrophy, with an incidence estimated at one per 10,000-50,000 live births. The defect of the abdominal wall results in an open, inside-out bladder with an exposed inner surface as well as a urethra with an epispadiac opening.

Epispadias patients have a mild defect compared to the other defects in the complex. The incidence of isolated epispadias is one per 100,000. Men present with a mucosal strip or an ectopic meatus on the dorsal part of the penis. Women present with a bifid clitoris, with variable degrees of a split in the urethra. A mild diastasis may be palpable if the symphysis is not closed. The umbilicus, rectus and abdominal wall anatomy is normal (3).

The cloacal exstrophy has the most severe presentation of the three variations and has an incidence of one per 200,000 live births. It is similar to the classic bladder exstrophy but the cecum or the most caudal part of the intestines splits the bladder into two inside-out surfaces. Another name for the cloacal exstrophy is the OEIS-complex; which means omphalocele-exstrophy-imperforate anus-spinal defects (3).

Clinical presentation

The classical bladder exstrophy presents with an inside-out bladder plate on the abdomen. This plate differs in size between individuals. Urine leaks from the ureters on the surface. When the patient is born, the mucosa looks red and mucosal polyps may be present. When the closure of the plate is delayed, more inflammation, ulcers as well as hyperplasia may occur. The umbilicus inserts on the upper margin of the bladder and is usually located lower than normal. The pubic symphysis is palpable on both sides of the bladder plate; a clear diastasis of the pubic bone is always present. Inguinal hernias are also common in both genders. The anal opening is usually more ventral than normal, although this usually has little clinical significance.

Males born with a bladder exstrophy have an open urethral plate that extends from the bladder plate to cover the dorsal side of the penis. The veru montanum is clearly visible and the bladder neck is poorly developed, as is the external sphincter complex. Both corpora
cavernosa are situated right below the urethral plate. The penis is bent dorsally, lacks the dorsal foreskin and the length of the corporal bodies is much shorter than normal (2-6).

Females have a bifid clitoris situated on both sides of the urethral plate. The labia majora are not fused on the superior part and have an anterior position. The labia minora are more lateral compared to their normal position. The vagina is narrower and shorter. The anus is located more ventrally than normal and the perineum is therefore shorter. They also have diastasis of the symphysis pubis (2,3,7).

Incidence

In the Netherlands 4-8 new patients with bladder exstrophy are born each year. This calculation is made based on the incidence.

Bladder exstrophy can be diagnosed as early as week 18 of pregnancy by means of ultrasound imaging. Together with Potter syndrome, bladder exstrophy is one of the many urological congenital diseases that can be diagnosed during pregnancy. This means that early counselling on this deformity is possible. The choice of termination of pregnancy can also be discussed with the parents. In a paper on prenatal detection of urologic anomalies in 12 European countries, it was found that 80% of parents chose to terminate the pregnancy after the foetus was diagnosed with bladder exstrophy (8).

Cervellione et al. conducted a study on the incidence of bladder exstrophy in 27 countries in 2010. Of the 6,650,300 babies that were born, 146 had bladder exstrophy. In that year 183,000 babies were born in the Netherlands and, according to his data, only 2 babies had bladder exstrophy. This research estimates the incidence of bladder exstrophy to be about 1:46,000 (9). No data were available on the number of pregnancies that were terminated because of bladder exstrophy.
Embryogenesis and aetiopathology

The normal embryology of the cloacal membrane and the defects that lead to bladder exstrophy are not completely understood. The endoderm in the embryo is responsible for the development of the gastrointestinal system. The caudal part of the primitive gut becomes sealed by the cloacal membrane.

The mesodermal growth of the cloacal membrane and the caudal migration will occur within 3 weeks of pregnancy. The mesodermal tissue forms the abdominal wall and is also responsible for forming the bony structures of the pelvis. Finally, the labiosacral swellings and the development of the genital tubercle will occur after the mesenchymal infiltration of the cloaca (10-13).

By 7 weeks of pregnancy, the relocation of the urorectal septum as well as the merging of the cloacal membrane will occur, leading to the formation of the perineal body. The cloacal membrane splits into two parts; the opening of the urogenital sinus will be formed by the anterior fragment and the rectum will be formed by the posterior part.

The urogenital sinus will form part of the bladder and part of the urethra that is situated in the pelvis. It will also contribute to the vaginal plate in women and to part of the urethra in the penis in men (10-15).

Figure 3: Diagram of the normal embryology of the cloaca and the cloacal membrane. a. Caudal growth of the urorectal septum splits the cloaca. B,c caudal migration of the cloacal membrane, fusion of the urorectal septum, followed by perforation leading to the anteriorly positioned urogenital opening and the posteriorly positioned anal opening.

The pathogenesis of bladder exstrophy is not completely understood. Marshall and Muecke introduced the most universally accepted theory, which suggests that the cloacal membrane develops abnormally, which hinders medial migration of the mesenchymal tissue to the midline (2,16,17). This malformation affects the lower abdominal wall muscles and the development of the pelvis, which results in an unstable cloacal membrane. One of the consequences is the herniation of the lower abdomen components, such as the urogenital system (2,18,19). There are many different studies about the embryogenesis of the bladder exstrophy. Austin et al. found that the abnormally developed cloacal membrane is indeed associated with bladder exstrophy (20). Currently, the most widely accepted theory is that of Mitchel et al. published in 1985, which is that the bladder exstrophy is not caused by the
overdeveloped cloacal membrane, but instead by the premature rupture of the cloacal membrane (13,21).

The timing of the premature rupture affects the severity of the outcome. The rupture of the cloacal membrane before 7 weeks of pregnancy results in a cloacal exstrophy, while a rupture after the urorectal septum has formed, around the 7th week of gestation, will result in a bladder exstrophy or an epispadias (22).

Boyadjiev et al. reported in their study, which includes 232 families with a child with an EEC-complex, that an older age of the parents has a significant association \( P < .001 \) with the complex. In 1984 Shapiro et al. recorded that inheritance of the EEC-complex is largely unknown. Smoking, alcohol and drugs are not risk factors for the EEC-complex (23-24).

**Surgical correction**

Most patients undergo a number of surgical procedures. The first operation, which is part of the Modern Staged Repair of bladder Exstrophy (MSRE), is performed shortly after birth. The goal of this first procedure is to close the bladder, reconstruct the pelvic ring, promote urinary continence and protect kidney function (19,17,25).

MSRE consists of three surgical reconstructions for boys, and two for girls. During the first procedure, the bladder and the abdominal wall will be closed. The diastasis of the symphysis, the pelvic floor and the bladder neck will be corrected as well. In girls, reconstruction of the epispadiac urethra, bifid clitoris and vaginal opening will be done in this procedure as well.

It is advised to operate within 48-72 hours after birth to take advantage of the flexibility of the pelvis of a newborn. When operating after 72 hours, pelvic osteotomies and longer immobilisation of the lower extremities is needed (12,19).

![Figure 4: MSRE stage I, a,b cut is made around the bladder plate and urethral plate to free them from the abdomen. c a ureteral stents and a suprapubic catheter are placed for the drainage of the bladder. The urethra is closed in an proper size. All structures are situated and fixated in the midline. The rectum and abdomen are closed. d,e the stents and catheter are brought out through the neoumbilicus](image-url)
The second reconstructive procedure is the epispadias correction in boys. This is usually performed when the boy is 1-2 years old. The third surgical intervention is done when the child fails to gain continence; it is therefore performed when the child is 4-6 years old. This most often includes a further reconstruction of the bladder neck, with ureter re-implantation when needed.

In bladder exstrophy, the ureters enter the bladder at an abnormal angle that, after the closure of the bladder, leads to vesico-ureteral reflux (VUR) in almost all patients. Re-implantation of the ureters usually takes place together with the reconstruction of the bladder neck, but may also be done as a separate procedure when the reflux leads to clinical problems such as febrile urinary tract infections and renal scarring (12,19,26). Bladder augmentation may be needed if the bladder capacity is not sufficient for the patient to become continent for urine. At present, this procedure is usually done in combination with bladder neck reconstruction and a continent catheterisable channel (12,13). Further reconstructive procedures may be necessary to obtain the best possible cosmetically and functionally acceptable genitalia (27).

The MSRE procedure has been used now for some 40 years, but before that period a number of different approaches were used. Closure of the bladder has always been part of the approach, but reconstruction of the bladder neck, the pelvic ring and external genitalia has known many different approaches and the outcomes of these procedures have not always been documented.

Many of the adult patients have eventually ended up with a urinary diversion, in order to achieve some form of continence and preservation of renal function (28,29).
The first applied method for urinary diversion in bladder exstrophy patients was Ureterosigmoidostomy (Coffey’s Ureterosigmoidostomy), where the ureters are implanted in the sigmoid, which results in the urine being in close contact with faeces. Provided the anal sphincter has adequate function, these patients can be continent for both urine and faeces. Coffey’s Ureterosigmoidostomy is no longer performed routinely because of the long-term risks, such as an increased risk of colorectal tumours, recurrent urinary tract infections, kidney stones and renal failure.

It is still an option for those patients with an extremely small bladder plate, or patients with inadequate medical care facilities such as in less developed countries (30-33).

In some patients the reconstructive procedures of the bladder and bladder neck have not resulted in sufficient urinary control and a urinary diversion has been performed (such as a ureteroileocutaneousostomy – Bricker) (34).

Nowadays new techniques have been explored and developed, such as a one-stage repair in the first year of life. In order to compare the results of newer approaches, it is absolutely necessary to have long-term outcome data of the procedures performed in the past – not only regarding continence outcome, but also regarding kidney function, number of re-operations, complications, sexual function, fertility issues and quality of life.

In this study the medical long-term outcomes, including continence and kidney function, have been addressed. An earlier study has addressed quality of life, sexual function and fertility issues.

**Long-term clinical outcomes**

**Urogenital tract**

After the closure of the bladder and the reconstruction of the bladder neck, it might be necessary to do additional procedures to achieve urinary “continence” (probably ‘dryness’ is a better term, as continence implies the ability to void spontaneously).

A well-established technique is bladder augmentation using a piece of small intestine to increase bladder capacity. Spontaneous voiding is no longer possible so the patients have to empty their bladders with intermittent catheterisation (CIC). This is sometimes possible through the urethra, but most patients prefer a suprapubic continent catheterisable channel. This is an extremely complex surgery and the number of complications is high. Before the surgery patients and their parents are told that 50% of all patients need at least one additional surgery during the first 10 years following the procedure. The most common complications are kidney and bladder stones, urinary tract infections (UTI), pyelonephritis, bladder perforations and difficulty performing CIC (1,35). Inouye et al. and Capolicchio et al. reported in their studies that urinary dryness was achieved after bladder neck reconstruction, bladder augmentation and a continent channel in 87-100% of all patients (35,36).

In all patients with urinary diversion or augmentation, metabolic changes may occur, such as vitamin B12 deficiency or hyperchloremic metabolic acidosis. Acidosis is only treated using bicarbonate, when the patient is symptomatic and hypercholaemic (37).
According to Ebert et al., one third of the EEC-complex patient population also have renal malformations, most commonly uretero-pelvic junction obstruction (UPJ stenosis), horseshoe kidney and an ectopic pelvic kidney (3). UTIs are as common in men as they are in women. The incidence of UTIs is reported to be 27% in the paper “Congenital Anomalies in Children: A Joint SIU-ICDU International Consultation” (1). An article by Mathews et al. included 83 women and indicated that 73% reported a UTI at the time of research (38).

According to Mathews et al., women are also prone to vaginal and uterine prolapse given that the pelvic ring does not provide enough support to the lower abdominal structures (38).

**Kidney function**

Any surgical procedure involving the bladder, bladder neck and ureters may lead to some form of obstruction of the upper urinary tract. Therefore the kidneys are at risk following these procedures (39,40).

**Measuring renal function**

Renal function is measured by calculating the GFR and creatinine levels. There are different formulas that could be used to estimate both of these. The two most commonly used formulas are the Modification of Diet in Renal Disease (MDRD) and the Cockcroft-Gault formula (41). A new formula was developed in 2009 which proved to be more accurate at measuring the estimated GFR (eGFR). It is called the CKD-EPI formula which stands for Chronic Kidney Disease Epidemiology Collaboration. This formula is highly accurate because, unlike the MDRD, the CKD-EPI does not underestimate kidney function of patients with a high eGFR. The CKD-EPI uses the same variables as the MDRD (i.e. body size, gender, age and creatinine levels) but it also takes ethnicity into account (42). CKD-EPI has been used in the UMCG since 2015 to measure eGFR and creatinine. The UMCG uses the following table (Table 1) as a frame of reference for GFR interpretations. The unit used in this table is ml/min/1.73m² (43).

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Median eGFR</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-40</td>
<td>Male</td>
<td>91</td>
<td>68-121</td>
</tr>
<tr>
<td>18-40</td>
<td>Female</td>
<td>82</td>
<td>63-106</td>
</tr>
<tr>
<td>41-50</td>
<td>Male</td>
<td>85</td>
<td>65-114</td>
</tr>
<tr>
<td>41-50</td>
<td>Female</td>
<td>77</td>
<td>57-104</td>
</tr>
<tr>
<td>51-60</td>
<td>Male</td>
<td>80</td>
<td>56-102</td>
</tr>
<tr>
<td>51-60</td>
<td>Female</td>
<td>74</td>
<td>56-99</td>
</tr>
<tr>
<td>61-70</td>
<td>Male</td>
<td>76</td>
<td>52-105</td>
</tr>
<tr>
<td>61-70</td>
<td>Female</td>
<td>69</td>
<td>48-101</td>
</tr>
<tr>
<td>&gt;70</td>
<td>Male</td>
<td>71</td>
<td>45-92</td>
</tr>
<tr>
<td>&gt;70</td>
<td>Female</td>
<td>67</td>
<td>46-96</td>
</tr>
</tbody>
</table>

Table 1: Normal measurements of eGFR according to CKD-EPI
The National Kidney Foundation Practice Guidelines for Chronic Kidney Disease state that an eGFR lower than 15 ml/min/1.73m$^2$ indicates renal failure (44).

**Relevance of this study**

Few papers describe the long-term outcome of patients born with bladder exstrophy. Most of these papers have addressed the psychosexual functioning of these patients (27,35,45,46), while only very few studies present data on renal function, urinary incontinence (40) or infectious complications (47).

According to the Dutch patient association of bladder exstrophy, there are approximately 300 adult patients born with bladder exstrophy in the Netherlands. So far only limited research has been conducted to analyse these problems among the Dutch exstrophy population. This study will focus on examining the long-term clinical outcomes of adult patients born with bladder exstrophy in the Netherlands, including renal function, urinary continence, urinary tract infections and the presence of stones.

In all patients with urinary diversion or bladder augmentation, blood gas analysis (pH), electrolytes level (particularly chloride) as well as vitamin B12 levels will be analysed.

**Objectives of this study**

The purpose of this study is to evaluate the long-term clinical outcomes after reconstructive surgery in patients born with bladder exstrophy treated at the UMCG.

Research questions:
1. Do patients born with bladder exstrophy have a normal kidney function, despite all reconstructive procedures?
2. Are these patients at risk of having more UTIs compared to the normal population?
3. Are these patients dry or do they still suffer from urinary incontinence despite all surgical procedures performed?

**Primary objectives:**

- To describe the renal function of the patients;
- To analyse the number of urinary tract infections of the patients during the past 5 years;
- To establish if the patients are dry or incontinent.

**Secondary objectives:**

- To assess pH and vitamin B12 level in those patients with urinary diversion or bladder augmentation;
- To determine if bladder augmentation is a risk factor for developing stones in the urinary tract in these patients.
Materials and methods

Research proposal

This research analyses the long-term clinical outcomes of all adult, living patients with bladder extrophy being followed at the department of Urology of the UMCG. The information will be retrieved from the medical files of the included patients.

This research is a UMCG-based project that is meant to become a national project including all patients born with bladder extrophy in the Netherlands. This national study is called: “Long-term results and sexual (dys)-function in patients with bladder extrophy in the Netherlands”.

This project started in 2015 and the first part studied the quality of life and sexual function of these patients. This second part studied renal function, urinary tract infections, urinary stones, metabolic abnormalities and urinary continence.

All patients who were contacted in 2015 have already signed an informed consent form. All patients who reached the age of 18 since 2015 were contacted this year, either during their appointment at the urology outpatient clinic or via a letter sent to their home explaining the reasons for this study. They were asked to sign the consent form and return it by mail.

Inclusion and exclusion criteria

The following inclusion criteria were set:
- Patients born with bladder extrophy, epispiadas or cloacal extrophy;
- Currently being followed-up by the department of Urology (UMCG);
- Older than 18 years at the moment of participation.

The following exclusion criteria were set:
- Death;
- Incomplete and missing information in the medical files;
- Unwillingness of the patient to participate.

Patient population

Of the 61 adult patients with bladder extrophy followed at the UMCG, 48 patients met the inclusion criteria; 2 patients had died and 11 were excluded for various reasons (incomplete medical information (10) or unwillingness to participate (1)).

Of the 48 patients, 6 had complete epispiadas, 39 a classical bladder extrophy and 3 were born with a cloacal extrophy.

Statistical analysis

The data were collected from the medical files of the patients (poliplus). Everything was registered in an Excel sheet and when the data were complete it was converted to an SPSS document for analysis. Some data were registered by splitting them into two groups (i.e. a yes and a no group), including the following: gender, having had a UTI, having a stone, being
incontinent and having had an ileal resection. The following data was reported in numbers and then checked for falling within the normal laboratory values: GFR, creatinine, urea, pH and vitamin B12. Finally, the types of urinary diversion and results of urine cultures were listed to provide an overview of the situation of the patients and whether the outcome of cultures was correlated to the clinical outcome, in particular regarding urinary stones.

Data registration and analysis was performed using the statistical package for the social sciences version 23.0 (SPSS Inc. Chicago, Illinois). Normal distribution of each variable was checked using the Q-Q plots. In case of normal distribution, the data were described using the mean plus or minus the standard deviation. The variables that were not normally distributed (i.e. age, creatinine and urea levels) were reported using the median plus the twenty-fifth and the seventy-fifth percentile. The correlation coefficient test was used to assess the correlation between the continuous variables. When a crosstab was used to compare the categorical variables, a chi-square test was included to be able to use the $p$-value of the Fisher’s exact test (2-sided).
## Results

<table>
<thead>
<tr>
<th>Gender of patients (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Men</td>
<td>27 (56.3)</td>
</tr>
<tr>
<td>- Women</td>
<td>21 (43.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median age (range*) at time of study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Actual range (youngest-oldest)</td>
<td>36 (27-50) yrs *25-75th percentile (18-75)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total dry patients (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Spontaneous voiding</td>
<td>33 (69)</td>
</tr>
<tr>
<td>- Coffey</td>
<td>3 (6.25)</td>
</tr>
<tr>
<td>- AMS sphincter</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>- CIC transurethral + dry</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>- Continent Catheterisable channel</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Indiana pouch</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>Cock pouch</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Mitrofanoff-/Monti-channel</td>
<td>18 (37.5)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Total incontinent patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinent stoma (Bricker)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Incontinent via urethra</td>
<td>9 (19)</td>
</tr>
<tr>
<td>CIC transurethral + leakage</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median serum creatinine (range)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Normal: Males: 50-110 umol/l</td>
<td>86 (73-100) umol/L</td>
</tr>
<tr>
<td>- Females: 50-90 umol/l</td>
<td>86 (±25.2) ml/min/1.73m²</td>
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</table>

<table>
<thead>
<tr>
<th>Mean GFR (±SD)</th>
<th></th>
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<tbody>
<tr>
<td>- See Table 1 for normal values</td>
<td>86.3 (±25.2) ml/min/1.73m²</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Median serum urea (range)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Normal for adults: 2.5-7.5 mmol/L</td>
<td>5.5 (4.42-6.9) mmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean systolic blood pressure (±SD)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean diastolic blood pressure (±SD)</td>
<td>127 (±13) mmHg</td>
</tr>
<tr>
<td>77 (±11) mmHg</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients who developed stones (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>16 (33)</td>
</tr>
<tr>
<td>- Kidney</td>
<td>3 (6)</td>
</tr>
<tr>
<td>- Bladder stones:</td>
<td>8 (17)</td>
</tr>
<tr>
<td>- Pouch stones</td>
<td>4 (8)</td>
</tr>
<tr>
<td>- Urethra</td>
<td>1 (2)</td>
</tr>
<tr>
<td>No</td>
<td>32 (67)</td>
</tr>
</tbody>
</table>
Number of people who experienced a urinary tract infection at least once a year in the last 5 years (%)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>15 (31.25)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Females</td>
<td>16 (33.33)</td>
<td>5 (10.41)</td>
</tr>
</tbody>
</table>

Number of patients who experienced three urinary tract infections per year (%)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 (18.8)</td>
<td>39 (81.23)</td>
</tr>
</tbody>
</table>

Number of patients with ileal resection for the purpose of urinary diversion or bladder augmentation (%):

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 (67.3)</td>
<td>13 (25)</td>
</tr>
</tbody>
</table>

Median Vit B12 for those with an ileal resection (range) Normal: for adults: 145-450 pMol/L
Mean pH for those with an ileal resection (±SD) Normal pH: 7.35 – 7.45
Median chloride levels in patients with acidosis (range)
Normal chloride: 97-107 mmol/L

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>228 (188-327) pMol/L</td>
</tr>
<tr>
<td></td>
<td>7.35 (±.04)</td>
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<tr>
<td></td>
<td>103 (101-104) mmol/L</td>
</tr>
</tbody>
</table>

Table 2: Descriptive data

Demographic information

The total number of patients is 48, 27 (56.25%) males and 21 (43.75%) females. The median age is 38 years and 34 years respectively. The mean age is 38.

Urination and urinary deviation

Three patients (6.25%) could urinate via the urethra without CIC, while three patients were incontinent via the urethra (complete incontinence vs. urge incontinence). Five patients use transurethral CIC, 2 of which are completely dry and 3 have leakage through the urethra. Twenty-five patients (52.1%) have a continent catheterisable channel and 9 (18.75%) patients have an incontinent diversion (Bricker).

Renal Function

Renal function was evaluated based on serum creatinine, serum urea and GFR. The majority of patients (85.41%) had a normal creatinine level compared to normal values for people of
the same age and gender. Four patients (8.33%) had a slightly higher than normal level, whereas three (6.25%) patients had significantly increased creatinine levels. One patient had undergone a kidney transplantation in 2009 and is still being followed; this patient has a Bricker urinary diversion.

GFR was evaluated according to the standards of the laboratory at the UMCG. The majority of patients (87.5%) had normal GFR levels. Three patients (6.3%) had slightly lower than normal levels, whereas one patient had a very low GFR of 13 ml/min*1.73 m2. The GFR of two out of the 48 patients was not available.

Serum urea was evaluated based on the normal level for healthy adults, which is from 2.5-7.5 mmol/L. Most patients (83.3%) had normal serum urea levels. Seven patients had a slightly higher than normal level, and one patient had an extremely high serum urea of 34.20. This patient has grade 5 renal failure.

<table>
<thead>
<tr>
<th>Between</th>
<th>Correlation coefficient</th>
<th>P value (P &lt; .05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and GFR</td>
<td>-.561</td>
<td>.000</td>
</tr>
<tr>
<td>Age and creatinine</td>
<td>.391</td>
<td>.006</td>
</tr>
<tr>
<td>Age and urea</td>
<td>.370</td>
<td>.010</td>
</tr>
</tbody>
</table>

Table 3: Correlation between age and renal function

According to Spearman’s test, there is a negative correlation (-.561) between the age of the patients and the level of their GFR. There is a positive correlation (.391) between creatinine levels and the age of the patients. There is a positive correlation (.370) between age and urea levels.

**Blood pressure**

Blood pressure was evaluated and the measurements of 9 patients were not available. The 39 other patients had a mean systolic pressure of 127 and a mean diastolic pressure of 77 mmHg. Five out of 39 patients are using anti-hypertensive drugs. One patient has high systolic blood pressure (156 mmHg) despite the use of anti-hypertensives.

**Urolithiasis**

Sixteen patients (33%) presented with stones at least once. The stones were mostly (25%) bladder or pouch stones, which were removed by cystolithotomy or endoscopically. One stone was located in the urethra. Finally there were 3 kidney stones, 2 of which were treated using Extracorporeal Shock Wave Lithotripsy (ESWL) and one stone passed spontaneously. Thirty-two patients did not experience urolithiasis.
Table 4: Association between Bladder augmentation and stone formation

Table 4 presents the presence of stones in the population divided into two groups, depending on whether they had had a bladder augmentation or not. As shown in Table 4, 13 of 35 patients with bladder augmentation developed stones, as opposed to 3 patients who developed stones without being augmented. According to the chi-square test, there is no association between having a bladder augmentation and developing stones.

**Urinary tract infections**

The number of patients who experienced a UTI at least once over the past five years was determined. Thirty-one patients (64.6%) had at least one UTI in the last 5 years, 9 (18.8%) of those patients had as many as three or more UTIs in the last three years. Whereas 17 patients did not experience any UTI in the past five years. The number of males and females who did experience a UTI was compared and it was 15 and 16 patients respectively. On the other hand, the number of males who did not have any urinary tract infection in the last five years was more than double that of females, 12 and 5 patients respectively.

Table 5 above compares the cases of UTIs in the last five years between men and women. There were 16 females who experienced at least one UTI in the last five years compared to 15 men. This difference is not statistically significant.

**Terminal ileum resection**

A total of 35 patients (67.3%) underwent ileal resection for the purpose of bladder augmentation or the creation of a catheterisable stoma. Vitamin B12 levels and venous pH were measured for these patients. A median of 228 was reported for the vitamin B12; only one patient was found to have a slightly lower than normal level (139 pMol/L) of vitamin
B12. The levels of vitamin B12 of 7 patients with an ileal resection were not available. As for the venous pH, a mean of 7.35 was reported. Twelve patients (46.2%) had acidosis varying from 7.34 to as low as 7.27. Only one patient with acidosis had a slightly higher than normal chloride level, though he was not symptomatic. None of the patients were prescribed bicarbonate.

<table>
<thead>
<tr>
<th>Bladder augmentation</th>
<th>pH level</th>
<th>Acidosis</th>
<th>total</th>
<th>Chi-square ((P &lt; .05))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>17</td>
<td>18</td>
<td>35</td>
<td>.414</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>22</td>
<td>20</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Association between bladder augmentation and pH levels

Table 6 examines the number of acidosis cases in this research group, comparing those with and without bladder augmentation. As shown in the table, 12 of the patients with a bladder augmentation had a lower pH than normal, whereas 8 of those without a bladder augmentation also had lower pH than normal. According to the chi-square test, this difference is not statistically significant.

**Urine cultures**

The latest urine cultures were analysed for bacteriology to find out the association with urolithiasis and the following was found: only one patient had stone-forming bacteria (Proteus), but this patient did not experience urolithiasis. The rest of the cultures presented E Coli (8 patients), the most common cause of UTI (which is mostly why the culture were taken).

<table>
<thead>
<tr>
<th>Urine culture outcomes</th>
<th>number</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>24</td>
</tr>
<tr>
<td>- E coli</td>
<td>8</td>
</tr>
<tr>
<td>- Streptococcus</td>
<td>3</td>
</tr>
<tr>
<td>- Proteus</td>
<td>1</td>
</tr>
<tr>
<td>- Mixed flora</td>
<td>6</td>
</tr>
<tr>
<td>- Divers</td>
<td>6</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
</tr>
<tr>
<td>No recent culture</td>
<td>10</td>
</tr>
<tr>
<td>available</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Urine cultures outcomes
Discussion

This study was conducted to investigate the long-term clinical outcomes of adult patients who had reconstructive surgery because of having a condition that falls under the EEC-complex. This study is the first of its kind in the UMCG. The analysis of this project’s population revealed that 83% had a normal renal function, 65% of the patients had at least one UTI in the last five years, and three patients are completely incontinent. Eighteen patients with bladder augmentation had acidosis and only one had a low vitamin B12 level. Of the patients with bladder augmentation, 13 experienced urolithiasis.

Renal function

Regarding the inspection of the renal function of the patient population, one case of kidney insufficiency was noted based on transplant failure caused by immunosuppressives toxicity. The rest of the patients had no signs of renal failure. Two men were excluded because of death. One man passed away as a consequence of an unresectable urothelial cell carcinoma in the right kidney at the age of 54 years. He had a sigmoid cancer in his medical history, possibly as a complication of a ureterosigmoidostomy. The other patient passed away at the age of 56 years, following a urosepsis due to a blow-out caused by a ureter stone obstruction. During the period of this research, one woman passed away. She was included because her death occurred after data collection and while doing the analysis. The cause of death was liver metastases of a late-stage bile duct cancer. Interestingly, both latter patients also had urinary stones.

According to Schaeffer et al., there is little information in the literature on the long-term clinical outcomes regarding renal function after modern operation techniques (40). Ebert et al. in Germany also suggest in their article that little research has been conducted regarding the long-term outcomes of surgical interventions (3).

In this research, a step was taken to evaluate the renal function, which was assessed based on GFR, creatinine and urea levels. Starting with the GFR, about 87.5% of the patients had a normal GFR rate at the time of measurement. This is comparable to what Schaeffer et al. found, which is that the renal function of most patients was not harmed by the staged reconstruction of the extrophy (40). What was done differently in this project is that the correlation between age and GFR was assessed. The correlation was negative, which according to laboratory measurements is not different from normal adults (43).

In “Long-term follow up of patients with bladder extrophy” Gobet et al. found that 60% of their population had creatinine levels within the normal range (39). In this research, however, the majority of patients (85.41%) had a normal creatinine level. The association between age and creatinine was tested as well. This association was positive but was not statistically significant. Regarding renal function, the population followed at the UMCG seems to be doing well.
Urinary tract infections

De Vries and Nijman’s publication “Congenital anomalies in children”, which is based on a systematic review, dedicates an entire chapter to bladder extrophy. Under the title ‘urinary tract infections’, 980 patients were included, of which around 27% reported a UTI (1). At the first line of medical care, the family physician practice in the Netherlands, UTIs are ranked as 8th on the list of most common complains leading to a doctor visit (47). The second national study into the diseases and procedures at the family physician practice in 2004 “De tweede Nationale Studie naar ziekten en verrichtingen in de huisartsenpraktijk-2004” reported the incidence of different diseases among which is urinary tract infections in the general Dutch population according to gender, recurrence percentage; per 1000 patients per year. They reported 7.7 for men and 58.5 for women with a recurrence percentage of 20% (48). In this study, the number of patients who had at least one UTI in the past five years was recorded which came down to a total of 64.6%, 18.8% of those patients had as many as there or more UTIs in the past three years. The total percentage of UTIs although in such a small group appears to be much higher in this research population than what is being reported in other literature. The association between UTIs and gender was tested and no significant difference was found. Almost the same exact number of men and women had a UTI in the past five years.

Incontinence

In “Congenital Anomalies in Children” by de Vries and Nijman, a systematic review of continence in bladder extrophy patients was performed as well. Continence was defined as follows “dry with voiding/catheterisation every 3 hours”. According to this definition, 51% out of 2711 patients included were reported continent for urine (1). Gupta et al. reported similar outcomes in a 20-year follow-up of 65 patients, where 50% were continent for urine (49). In this study, patients were divided into two groups: continent by urethra, stoma or ureterosigmoidostomy and incontinent via urethra or stoma. Based on this division, 69% of the described population is continent to urine. Even though the number of patients is relatively small, they seem to do better than reported in the literature.

Terminal ileal resection

When bladder augmentation is performed, a piece of the small intestine, namely the terminal ileum, is used to expand the bladder, or make a pouch. When this is done, urine comes in regular contact with a piece of intestine that might absorb substances that increase the acidity of the blood (37).

Austin studied metabolic complications in those with a bladder augmentation and stated that the rate of acidosis is very minimal given the small segment of intestine that is being used for augmentation versus a larger segment for a neobladder (50). While a total of 41.7% of our study patients had a decreased pH, 18 patients (37.5%) had an augmented bladder; this is in contrast to 2 patients (4.2%) with a native bladder who also had a decreased pH. Although the percentage of patients with acidosis in our study group is higher than that reported in the literature, there was no significant association between bladder augmentation and acidosis (P = .414).
Normally speaking, vitamin B12 is absorbed in the terminal ileum. Thus, when it is used for bladder augmentation, there may be vitamin B12 deficiency in the long run (37). Blackburn et al. looked into vitamin B12 deficiency in 105 patients after ileal bladder augmentation; 2 (2%) patients were vitamin B12 deficient (51). A similar percentage was found in our study population, where only 1 patient with an augmented bladder was vitamin B12 deficient. The association between bladder augmentation and B12 deficiency was tested and was not found to be statistically significant in this group ($p = .431$). However, vitamin B12 check-ups will continue once per year as recommended in the literature (51).

Another risk that appears is the formation of bladder or pouch stones (51,52). Inouye et al. reported that both patients with a native bladder and an augmented bladder experienced bladder stones, 29.4% and 28.4% respectively (35). In this study, the total number of patients who experienced stones was 16 (33%); 3 (6%) of those patients had a native bladder and 13 patients (27.1%) had an augmented bladder. Of the 13 patients with an augmented bladder, 10 had a bladder stone, while the other 3 had kidney stones. On the other hand, a total of 32 (67%) patients did not experience any stones, of which 22 had an augmented bladder. The association between having had a bladder augmentation and having a stone was tested and the result was not statistically significant. The patients with an augmented bladder do not have more stone formation than the non-augmented patients.

**Limitations and suggestions**

Although many results of this study are comparable to those in the literature, there were some differences found. One of the reasons could be the limited number of participants, as only 48 patients were included. We hope to increase the number when the study opens up for all adult bladder extrophy patients in the Netherlands. Another factor could be that this was a retrospective study; all the information was retrieved from the medical records of the patients. This could lead to selection bias, and a number of laboratory results were not available for some patients. The nature of this study project was mostly descriptive. Regarding the urological state of the patients, percentages were reported and the correlation and/or association of some of the variables were tested. A next step could be to compare those patients to a healthy control group. Renal function was evaluated solely based on laboratory results; the ultrasound images (although available) were not taken into account. Ultrasound images should be taken into account to improve the interpretation of the kidney function. Moreover, many patients from different age groups were included. This led to a variety in the type and number of procedures they underwent, which could have had a significant impact on their functioning. However, the number of patients is too limited to divide them into groups based on the type and number of operations they have had.

**Conclusion**

Based on this research, it can be concluded that surgical correction of bladder extrophy does not have a negative influence on renal function, nor does it lead to stone formation or vitamin B12 deficiency in the long term. Although no correlation was found between acidosis and bladder augmentation, more than one third of our patients should be closely followed for acidosis and other metabolic changes. This study population reported a higher percentage of urinary tract infections than occurs in the Dutch population, with no preference for either gender. Finally, it seems that a great number of patients are dry and do not suffer from urinary incontinence.
References


(38) Mathews RI, Gan M, Gearhart JP. Urogyneacological and obstetric issues in women with the exstrophy-epispadias complex BJU Int 2003;91(9):845-849.


(48) van der Linden, MW., Westert G, de Bakker D. De Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. NIVEL/RIVM 2004:64. Available at: https://www.nivel.nl/sites/default/files/bestanden/ns2_rapport1.pdf


