Cloacal Malformations

When all ends meet

HENDT VERSTEEGH

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Hendt Versteegh

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Contents

Chapter 1

General introduction

General introduction

Cloacal malformations are among the most complex congenital anomalies involving the pelvic organs in females. Cloacal malformations have an incidence of 1:50,000 newborns, comprising approximately 10% of all anorectal malformations, which seem to occur 1:3,000-5,000 newborns.[1] In this chapter short overviews of both normal, and affected anatomy and embryology are given. Furthermore, etiology, classifications, and therapeutic strategies are addressed.

Normal anorectal and urogenital anatomy in females

In normal female anatomy the rectum, vagina, and urethra all have separate openings to the perineum (Fig. 1.1). The rectal opening, the anus, is found posteriorly. The anal canal is surrounded by sphincter muscles (internal and external) to assure a certain rest pressure to close the canal and to voluntary release pressure in case of defecation.[2] Next to the presence of voluntary sphincter muscles, anal canal sensation and colonic motility are needed in order to achieve fecal continence.[3] Anteriorly to the rectum and anus, the female genital organs are found. These organs, the vagina and uterus, are connected to the vestibulum through the vaginal introitus. Slightly more anteriorly in the vestibulum the opening of the urethra is found. The urethra is the tubular structure running from

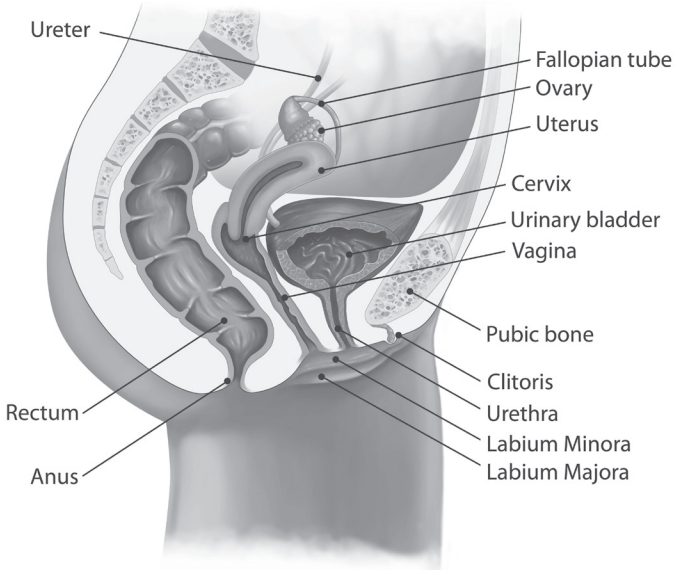

Figure 1.1 *Normal pelvic anatomy in the female*

the urinary bladder to the vestibulum. The connection between the urethra and bladder is called the bladder neck. All organs within this pelvic region are surrounded by several ligaments and muscles, referred to as the pelvic floor. The pelvic floor is essential in maintaining solidity of the pelvic organs and keeping normal function of these organs, with the levator ani muscle as most important structure in supporting the pelvic organs, and to assure urinary and fecal continence.

Embryologic development of the pelvic organs

In normal human embryology a structure called cloaca is present between the 3rd and 7th week of development.[4,5] This embryological cloaca is entered cranially by the hindgut (future distal bowel, posteriorly) and anteriorly by the future urogenital tracts (allantois/bladder precursor, Wolffian duct and Müllerian duct). It is separated from the amniotic cavity by a structure called the cloacal membrane. During cloacal development a septum dividing the allantois and hindgut, the urorectal septum, grows towards the cloacal membrane. The two, however, will never meet as the cloacal membrane denatures as a consequence of apoptosis, and the distal urorectal septum will grow out to form the perineum. The precise outgrowth of the normal anorectal region is still a matter of debate.[6] One theory proposes a process involving septation of the embryological cloaca with lateral ridges fusing with the urorectal septum and therefore dividing the cloaca in an anterior (urogenital) and a posterior (anorectal) part. The other theory has it that the rectal opening is found more anteriorly during early embryology and shifts towards its posterior future position afterwards. Both remain theories, however, and have never been proven by either animal or human embryological studies.[6]

Failure of the anal canal to develop normally and in normal position results in anorectal malformation. A during recent years widespread theory of the occurrence of anorectal malformations is one stating that these malformations represent 'frozen stages' of normal embryology.[7] Regarding cloacal malformations, however, such a stage in which embryonic development may have stopped and would have resulted in the anomaly as seen in neonates, has never been found in any of the studies conducted with human or animal embryos.[6] In spite of the similar nomenclature, embryological cloacas and cloacal malformations are two distinct anatomical states.

A more recent theory excludes the above stated hypothesis.[6] In that theory, the posterior part of the cloacal membrane represents the future anal orifice. In rat models this specific part of the cloacal membrane is in a fixed position during development without migrating elsewhere (Fig. 1.2). Therefore it is concluded that in normal anorectal devel-

opment the location and precursor of the future anal orifice are present throughout development and fixed at the most dorsal cloacal membrane. Rat models in which the cloacal membrane is shorter than in normal development are the first ever to mimic anorectal malformations as they appear in the human condition (Fig. 1.3). In these models the rectal opening is still found near the most posterior cloacal membrane, and in case of a short membrane this opening is found in the urogenital sinus.

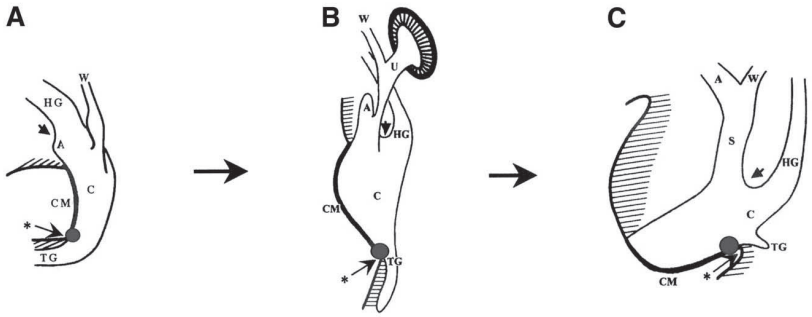

Figure 1.2 *Schematic drawing of normal cloacal development in rats. (A) A 12.5-day embryo; (B) 14-day embryo; and (C) 15-day embryo. Note the shift of the cloacal membrane (CM) from a vertical to a horizontal position. This movement is caused by the ventral outgrowth of the genital tubercle and the cloaca. Note the descent of the urorectal fold or septum (short arrows). The dorsal part of the cloacal membrane (gray dots) is the area of the future anal opening. Arrows with asterisk (*) point to the tail groove. This area is the fixed point in development of the cloaca. HG Hindgut; CM cloacal membrane; C cloaca; TG tail gut; A allantois; S sinus urogenitalis; W wolffian (mesonephric) duct; U ureter. Permission to reproduce figures from original source6 was granted by copyright owner.*

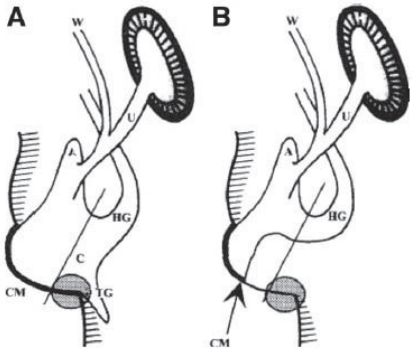

Figure 1.3 *Schematic drawing of a normal (A) and an abnormal (B) cloaca. In the abnormal embryo, the cloacal membrane (CM) is too short (arrow). The cloacal membrane does not extend to the region of the tail groove (gray area). The dorsal cloaca is missing. In the normal embryo (A), the cloacal membrane is of normal length and extends to the region of the tail groove. Permission to reproduce figures from original source6 was granted by copyright owner.*

Anorectal malformations

Anorectal malformations are all congenital anomalies in which the anal canal has not formed at all, or has not formed properly. A mild manifestation is the anal stenosis, which may go undiagnosed for several years, if diagnosed at all. In more severe cases the anus has not been formed, which is often associated with an abnormal connection between the rectum and another structure, which connection is called a rectal fistula. In females these anomalies comprise a wide spectrum. One end of this spectrum is the rectoperineal fistula, characterized by a fistulous connection between the rectum and the perineal skin anterior to where the anal orifice should have been and where, in most cases, the external anal sphincter complex can be found (Fig. 1.4A). The spectrum continues with the rectovestibular fistula, with the fistula opening just outside the posterior vaginal wall in the vestibulum (Fig. 1.4B). The other end represents the most severe anorectal malformation in females, the cloacal malformation, in which the rectum, vagina, and urethra drain into one common channel with its opening usually positioned where the vaginal introitus may be expected (Fig. 1.4C). While it is a distinct malformation, the

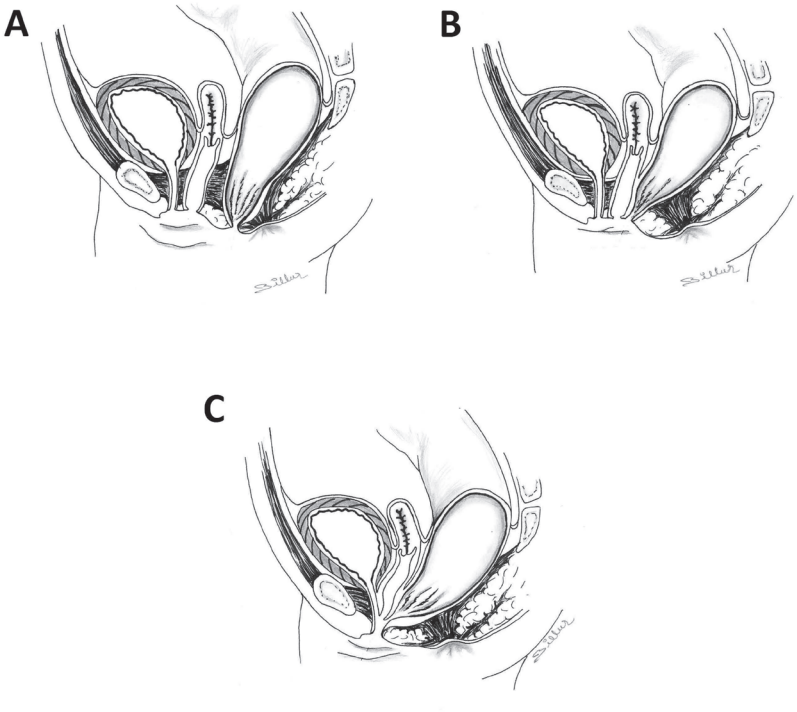

Figure 1.4 *Drawings of the most common female types of anorectal malformation. (A) rectoperineal fistula; (B) rectovestibular fistula; (C) cloacal malformation.*

rectovaginal fistula without further urethral anomalies is not included in this spectrum of common anorectal anomalies, as it only very rarely occurs as congenital anomaly.[8] Besides this anomaly the classification of anorectal malformation includes several other rare anomalies, such as H-type fistulas, and rectal atresias or stenosis.[9] For males a similar spectrum of 'common' malformations is known, ranging from a rectoperineal fistula and a bulbar rectourethral fistula, to a prostatic rectourethral fistula and, the most complex, rectobladderneck fistula; but this is out of the focus of this thesis.

Etiology of cloacal malformation

Causes of cloacal malformations – and anorectal malformations in general – are thought to be genetic, environmental, or a combination of both. The cases that are thought to be of genetic origin can be divided in syndromic and non-syndromic cases. Ten percent of patients with an anorectal malformation are individuals with syndromic conditions (e.g. Down syndrome), although a clear link of chromosome 21 leading to anorectal malformation has never been identified. For the majority of patients with anorectal malformation the etiology is not clear.[10] The non-syndromic anorectal malformation is found in isolated form but also in combination with one or more anatomical malformations. The combined form is seen in approximately 40-70% of patients.[10] Most of the associated malformations are found within the wide spectrum of the VACTERL association; this acronym derives from Vertebral, Anal, Cardiac, Tracheo Esophageal, Renal, and Limb abnormalities. The presence of at least three of these anomalies is generally considered necessary for the diagnosis of this condition.[11] The presence of associated anomalies may affect initial therapy, as generally the most life-threatening condition will be given highest priority. The presence of associated anomalies may affect outcome as well as it is associated with a higher mortality rate. Several studies were conducted to identify candidate genes involved in embryogenesis, such as genes in the sonic hedgehog pathway, possibly involved in non-syndromic anorectal malformation etiology, but none of these studies revealed a clear link.[10, 12-14]

Besides genetic factors, several non-genetic factors have been suggested to be associated with risk of anorectal malformations. Factors such as assisted reproductive techniques, multiple birth, preterm delivery, low birth weight, maternal obesity, and preexisting maternal diabetes mellitus were found to be consistently associated with anorectal malformations.[10] Note that there is merely an association; a causal relationship between those factors and the occurrence of congenital anorectal malformations has not been established. Clear evidence of an association with anorectal malformation etiology specifically has never been found, therefore it is concluded that the majority

of cases most likely are of multifactorial origin, combining genetic and non-genetic factors.[10]

Classification systems and follow-up

The first report of classification systems for anorectal malformations was published as early as 1749 by Heister.[15] New classification systems have been introduced meanwhile and until 2005 the Wingspread classification was most widely used.[16] Although it has a separate heading for cloacal malformations, this classification mainly distinguishes low, intermediate, and high anorectal malformations. Artificial lines just above or just below the levator ani muscle would classify the malformation. The Wingspread system was criticized, as the divisions into high, intermediate and low are often arbitrary, and because each group included defects with different therapeutic and prognostic implications. This problem was eventually solved with the introduction and implementation of the Krickenbeck classification in 2005 (Fig. 1.5).[9] This classification distinguishes each type of ARM from another based on anatomical differences and therapeutic consequences, and is based on both clinical findings and also includes a classification for the reporting of functional outcomes.

Even before the introduction of the Krickenbeck classification the cloacal malformation was considered a separate entity and the most severe female type of anorectal malformation. It was not until the introduction of the Krickenbeck classification, however, that more reports on different types of ARM started to appear in the international medical literature. Although outcome studies in patients with cloacal malformations are still scarce, studies gradually did show that cloacal malformations should be classified as

Krickenbeck classification for anorectal malformations

Major clinical groups	Rare/regional variants
Perineal (cutaneous) fistula	Pouch colon
Rectourethral fistula	Rectal atresia/stenosis
Prostatic	Rectovaginal fistula
Bulbar	H-type fistula
Rectovesical fistula	Others
Vestibular fistula	
Cloacal malformation	
No fistula	
Anal stenosis	

Figure 1.5 *The Krickenbeck classification. International standard for diagnosis of anorectal malformations.*[9]

either simple (short common channel) or complex (long common channel), with especially the latter type being more severe and with worse clinical outcome compared to perineal fistulas and vestibular fistulas.[3,17] Furthermore, cloacal malformations can be distinguished according to their further anatomical qualities, such as uterus anomalies (e.g. didelphys or bicornis), as well as length of the urethra (between common channel and bladder neck). The majority of previous studies on cloacal malformation outcome focused on colorectal outcome, such as fecal incontinence or constipation. However, as the cloacal malformation involves not only the colorectal tract but also the urological and gynecological tracts, it is not unreasonable to suggest that other types of outcomes should be reported as well.

Neonatal surgical management

The current neonatal management of patients with cloacal malformations has been well described in current literature.[18,19] In all cases the emphasis should lie on draining any fluid collections or obstructions present in gastrointestinal, urological, and gynecological tracts (hydrocolpos). In addition, the presence or absence of associated anatomical anomalies should be investigated, notably VACTERL association. Also, the exact details of the cloacal malformation should be assessed, since length of the common channel and length of the urethra are decisive for the procedure chosen for surgical reconstruction. In general, the first surgical procedure is conducted on the first day of life with the creation of a diverting colostomy to prevent any obstruction of the distal gastrointestinal tract and if necessary placing drains in urologic and gynecological tracts. The primary reconstruction of the cloacal malformation can and will then be postponed until the time both the parents and the surgical team feel most ideal.

Surgical correction of cloacal malformations

The most widely used surgical procedures today are the ones proposed by Dr. Alberto Peña in 1982 and 1997. In 1982 he introduced the posterior sagittal approach – fully named Posterior Sagittal AnoRectoPlasty (PSARP) – for the reconstruction of anorectal malformations.[20,21] In this procedure the patient is in prone position and dissection would be in the midline strictly. For cloacal malformations in particular this technique was extended to the Posterior Sagittal AnoRecto Vagino UrethroPlasty (PSARVUP) in 1989.[22] After a strict midline incision, cleaving the pelvic floor musculature, identifying, dissecting and mobilizing the rectum, this technique consisted of dividing the urogenital sinus in a urethral part to create a neo urethra and a dorsal vaginal part to construct,

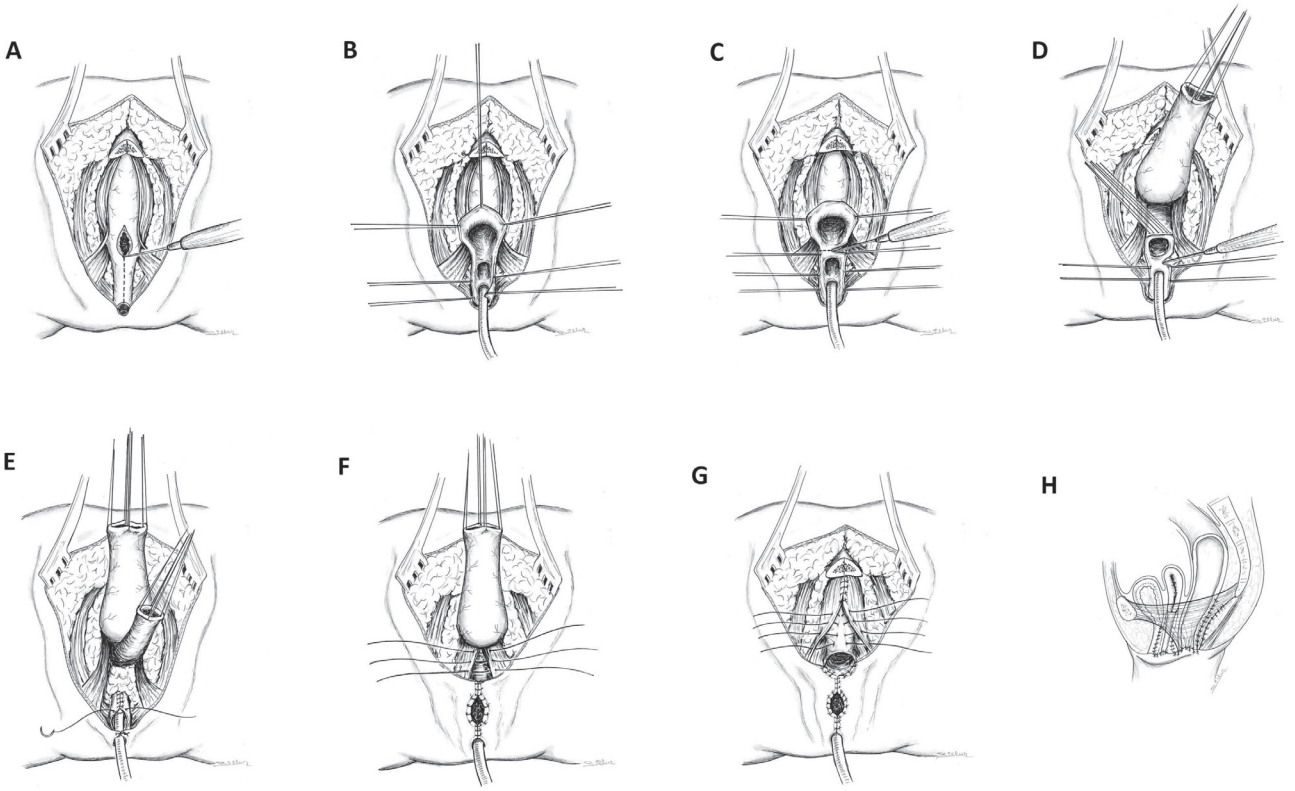

Figure 1.6 *Posterior sagittal anorecto vagino urethroplasty (PSARVUP). A. Sagittal incision from sacrum to common channel opening, identifying and opening rectum; B. Identifying rectal, vaginal, and urethral openings; C. Dividing of rectal fistula; D. Mobilizing rectum and dividing common channel in anterior urethral part and dorsal vaginal part; E. Mobilizing (neo) vagina, reconstruction of urethra; F. Reconstruction of (neo) vagina and perineal body; G. Construction of neo anus and perineal body; H. Sagittal view of post reconstruction anatomy.*

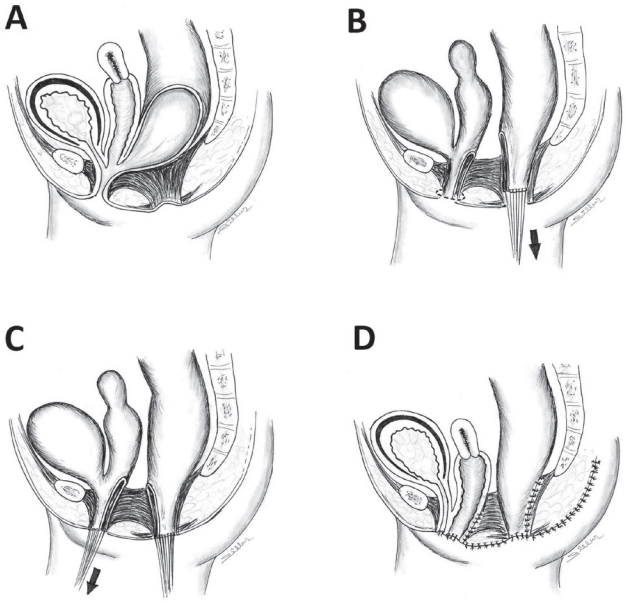

Figure 1.7 *Total urogenital mobilization (TUM). A. Preoperative anatomy; B. Identification and mobilization of rectum; C. Mobilization of urogenital sinus; D. Perineal reconstruction with creation of neo anus.*

when possible, a neo vagina (Fig. 1.6A-H). In 1997 Dr. Peña introduced a new technique, the Total Urogenital Mobilization (TUM). In this procedure the urogenital sinus was no longer divided, but rather mobilized *en bloc* to create mobility in order to reach the perineum (Fig. 1.7A-D).[23] The TUM procedure was presented as leading to better cosmetic results and shorter operation time. However, it has some limitations such as a maximum length of the common channel and a suitable urethral length between common channel and bladder neck to serve as a future urethra from bladder to perineum. Nevertheless, both the PSARVUP and the TUM are still being used for reconstructive surgery in cloacal malformations.

Aims of this thesis

The studies presented in this thesis aimed to evaluate both surgical as well as post-operative treatment of patients with cloacal malformations in the Netherlands in the past 25 years. Although a few other studies regarding long-term outcome after cloacal malformation surgery have been presented in the past, none of these aimed to assess a nationwide population nor did many of them assess all anatomical tracts involved in the cloacal anomaly.[24-28] We aimed to achieve the first nationwide assessment of the long-term follow up of this rare and complex malformation in all its aspects. Particular emphasis was placed on the impairments related to the various fields of medicine involved (surgical, urological, gynecological, and psychological). Furthermore, we investigated the necessity of adapting the multidisciplinary approach for patients with anorectal malformations in general to the special needs of cloacal malformation patients.

Outline of this thesis

In **Chapter 2** we provided an overview of the current literature on clinical outcome in patients with cloacal malformations as published in peer-reviewed international medical journals. This systematic review of literature was conducted according to internationally, evidence-based guidelines for the preferred reporting in systematic reviews.[29]

A nationwide assessment was conducted regarding the clinical outcomes of patients born with cloacal malformations in the Netherlands during the past 25 years. In **Chapter 3** the database that resulted from this assessment was used to study the possible influence of the age of the patient at which cloacal reconstruction is performed with a special emphasis on postoperative complications and colorectal outcome. The different surgical techniques used for cloacal malformation surgery and their influence on urological outcomes were studied in **Chapter 4**.

In **Chapter 5** we investigated the possible consequences of surgery used for reconstruction of anorectal malformation in regard of bladder function using preoperative and postoperative urodynamic studies in a group of patients with cloacal malformation or other types of anorectal malformation.

Chapter 6 presents an overview of the literature on postoperative complications after cloacal reconstruction and on the need for surgical interventions, both of which are known to influence outcome. This chapter also assesses the occurrence of complications after different surgical techniques used for cloacal malformation surgery.

In **Chapter 7** quality of life reported by patients with cloacal malformation and their parents with the use of questionnaires was compared to quality of life as reported by patients with other types of anorectal malformations, and their parents. The ultimate aim of this study was to consider whether adjustments in the regular anorectal malformation follow up would be needed for patients with cloacal malformations, which is thought to be a more complex condition.

Chapters 8 and 9 serve as a general discussion, taking a second look on the findings in previous chapters, and a summary of this thesis, respectively.

References

1. Warne SA, Hiorns MP, Curry J et al. Understanding cloacal anomalies. Arch Dis Child 2011; 96: 1072-1076.
2. Stoker J. Anorectal and pelvic floor anatomy. Best Pract Res Clin Gastroenterol 2009;23: 463-475.
3. Levitt MA, Pena A. Anorectal malformations. Orphanet J Rare Dis 2007; 2: 33.
4. Nievelstein RA, van der Werff JF, Verbeek FJ et al. Normal and abnormal embryonic development of the anorectum in human embryos. Teratology 1998; 57: 70-78.
5. Nievelstein RA, Vos A, Valk J et al. Magnetic resonance imaging in children with anorectal malformations: embryologic implications. J Pediatr Surg 2002; 37: 1138-1145.
6. Kluth D. Embryology of anorectal malformations. Semin Pediatr Surg 2010; 19: 201-208.
7. Schwalbe E. The morphology of the malformations in human and animals. Part 1: General Teratology. Jena, Germany: Gustav Fischer 1906: 143-144.
8. Lawal TA, Chatoorgoon K, Bischoff A et al. Management of H-type rectovestibular and rectovaginal fistulas. J Pediatr Surg 2011; 46: 1226-1230.
9. Holschneider A, Hutson J, Pena A et al. Preliminary report on the international conference for the development of standards for the treatment of anorectal malformations. Journal of Pediatric Surgery 2005; 40: 1521-1526.
10. Wijers CH, van Rooij IA, Marcelis CL et al. Genetic and nongenetic etiology of nonsyndromic anorectal malformations: a systematic review. Birth Defects Res C Embryo Today 2014; 102: 382-400.
11. Solomon BD. VACTERL/VATER Association. Orphanet J Rare Dis 2011; 6: 56.
12. Dworschak GC, Draaken M, Marcelis C et al. De novo 13q deletions in two patients with mild anorectal malformations as part of VATER/VACTERL and VATER/VACTERL-like association and analysis of EFNB2 in patients with anorectal malformations. Am J Med Genet A 2013; 161A: 3035-3041.
13. Bartels E, Draaken M, Kazmierczak B et al. De novo partial trisomy 18p and partial monosomy 18q in a patient with anorectal malformation. Cytogenet Genome Res 2011; 134: 243-248.
14. van de Putte R, Wijers CH, de Blaauw I et al. Sequencing of the DKK1 gene in patients with anorectal malformations and hypospadias. Eur J Pediatr 2015; 174: 583-587.
15. Yesildag E, Muniz RM, Buyukunal SN. How did the surgeons treat neonates with imperforate anus in the eighteenth century? Pediatr Surg Int 2010; 26: 1149-1158.
16. Stephens F. Anorectal malformations in children: update 1988. March of Dimes Birth Defect Foundation Original series 1988; 24.
17. Levitt MA, Pena A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg 2010; 19: 128-138.
18. Pena A, Levitt MA. Surgical management of cloacal malformations. Semin Neonatol 2003; 8: 249-257.
19. Pena A, Grasshoff S, Levitt MA. Reoperations in anorectal malformations. J Pediatr Surg 2007; 42: 318-325.
20. deVries PA, Pena A. Posterior sagittal anorectoplasty. J Pediatr Surg 1982; 17: 638-643.
21. Pena A, Devries PA. Posterior sagittal anorectoplasty: important technical considerations and new applications. J Pediatr Surg 1982; 17: 796-811.

22. Pena A. The surgical management of persistent cloaca: results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg 1989; 24: 590-598.

23. Pena A. Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997; 32: 263-267.

24. Warne SA, Wilcox DT, Creighton S et al. Long-term gynecological outcome of patients with persistent cloaca. J Urol 2003; 170: 1493-1496.

25. Warne SA, Wilcox DT, Ransley PG. Long-term urological outcome of patients presenting with persistent cloaca. J Urol 2002; 168: 1859-1562.

26. Rink RC, Herndon CD, Cain MP et al. Upper and lower urinary tract outcome after surgical repair of cloacal malformations: a three-decade experience. BJU Int 2005; 96: 131-134.

27. Kubota A, Nara K, Kawahara H et al. Therapeutic strategy for persistent cloaca: the efficacy of antegrade continent enema as a salvage surgery. Pediatr Surg Int 2011; 27: 505-508.

28. Leclair MD, Gundetti M, Kiely EM et al. The surgical outcome of total urogenital mobilization for cloacal repair. J Urol 2007; 177: 1492-1495.

29. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.

Chapter 2

Long-term follow-up of functional outcome in patients with a cloacal malformation: a systematic review

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René MH Wijnen
Ivo de Blaauw

Journal of Pediatric Surgery 2013; 48: 2343-2350.

Abstract

Background Reconstructive surgery is performed in patients with cloacal malformations to achieve anorectal, urological, and gynecological function. The aim of this study was to evaluate the functional outcome of cloacal malformation repair as reported in literature.
Methods A systematic literature search was conducted according to PRISMA guidelines using PubMed, EMbase and Web-of-Science. Records were assessed for the reporting of functional outcome, which was divided in anorectal, urological, or gynecological function. Studies were used in qualitative (Rangel score) and quantitative syntheses.
Results Twelve publications were eligible for inclusion. Voluntary bowel movements were reported in 108 of 188 (57%), soiling in 146 of 205 (71%), and constipation in 31 of 61 patients (51%). Spontaneous voiding was reported for 138 of 299 patients (46%), 141 of 332 patients (42%) used intermittent catheterization, and 53 of 237 patients (22%) had a urinary diversion. Normal menstruations were reported for 25 of 71 patients (35%). Centers with limited experience reported similar outcome compared to centers with more experience (≥1 patients/year).
Conclusion In this review we present functional outcome of the largest pooled cohort of patients with cloacal malformations as reported from 1993 to 2012. Functional disturbances are frequently encountered in anorectal, urological, as well as gynecological systems. Reporting of functional outcome in these patients should improve to increase knowledge about long-term results in patients with this rare malformation and to reach higher study quality. Especially, sacral and spinal anomalies should always be reported given their impact on functional outcome. Specialized care centers may be of great importance for patients with rare and complex conditions.

Introduction

A cloacal malformation is one of the most complex congenital anorectal abnormalities and still is one of the most challenging procedures in pediatric surgery. A cloacal malformation is defined as a urethra, vagina, and rectum that remain fused during the early stages of embryological development.[1] Occurring once in every 20,000-25,000 newborns, it accounts for approximately 10% of all anorectal malformations.[2,3]

Surgical therapy for cloacas changed considerably with the application of the posterior sagittal approach in 1982[4,5], and again with the introduction of the total urogenital mobilization in 1997.[6] The reconstruction of cloacal malformations became more anatomically precise, operation time was reduced, and there were fewer postoperative complications.[6,7]

In the early years of successful surgical management of cloacal malformations studies focused on short-term results of fecal and urinary continence of the different surgical approaches. In more recent years longer-term fecal and urinary functional outcome of patients with cloacal malformations were reported, as well as reproductive outcomes such as having a normal and reproductive sexual life. However, most studies present small numbers of patients due to the malformation's rarity. Furthermore, many studies present their patients with cloacal malformations as a part of the group of patients in larger studies of anorectal malformations. Finally, many different modes of scoring systems have been used making comparison of studies difficult and associated sacral and spinal anomalies are rarely mentioned. A good overview of the final outcome of all three systems (anorectal, urological, and gynecological) is still lacking. Therefore, a systematic review was performed to analyze all current literature on long-term functional outcome in the three areas that are congenitally malformed by the cloacal malformation.

Methods

Guideline

The PRISMA statement, checklist and flow-chart were used in order to achieve the highest standard in reporting items for a systematic review and meta-analysis.[8,9]

Search strategy

A systematic literature search was conducted on November 11th, 2011 using the PubMed, EMbase, and Web-of-Science databases. Studies were searched in PubMed using the following search terms: ((((cloaca[mesh] NOT enterobacter[mesh]) OR anus,

imperforate[mesh]) AND (surger*[tw] OR surgic*[tw] OR operat*[tw] OR reconstruct*[tw]) AND (outcom*[tw] OR effic*[tw] OR continen*[tw] OR incontinen*[tw] OR soil*[tw] OR catheter*[tw] OR constip*[tw] OR obstipat*[tw] OR menstruat*[tw] OR void*[tw]) NOT (animals[mesh] NOT humans[mesh])) OR ((cloaca*[tw] OR anus*[tw] OR anal[tw] OR anorect*[tw] OR urorectal*[tw] OR rectal*[tw] OR rectum*[tw] OR urogenit*[tw] OR urologic*[tw] OR vagina*[tw]) AND (malform*[tw] OR anomal*[tw] OR imperforat*[tw]) AND (surger*[tw] OR surgic*[tw] OR operat*[tw] OR reconstruct*[tw]) AND (outcom*[tw] OR effic*[tw] OR continen*[tw] OR incontinen*[tw] OR soil*[tw] OR catheter*[tw] OR constip*[tw] OR obstipat*[tw] OR menstruat*[tw] OR void*[tw]) NOT (animals[mesh] NOT humans[mesh]) NOT medline[sb])). For the other databases similar search terms were applied which concerned the functional outcome of patients operated on cloacal malformations.

Eligibility criteria

All written studies in English that reported postoperative functional outcome of patients with a cloacal malformation were included. Functional outcome was defined as anorectal, urological, or gynecological. No limits were set with regard to date of publication. Studies on cloacal exstrophies and the cloacal dysgenesis sequence were excluded, as well as all case-studies or studies presenting less than 5 patients. Studies about the subject of anorectal malformations in general were only included when presenting at least 5 patients with a cloacal malformation and when results of these patients were reported separately from the results of the patients with other anorectal malformations. The references of each of the articles we found were also reviewed to include useful studies that might have been missed with the initial literature review. Different articles that presented identical variables of the same study population were excluded, and the most recent publication, the publication presenting the largest sample or the most outcome variables was chosen.

Study selection

The study selection consisted of four separate processes; 1. Study identification, 2. Study screening, 3. Study eligibility, 4. Study inclusion. All processes were conducted by two separate reviewers (HV, IdB).

Quality assessment

Quality of the articles was scored using the checklist as proposed by Rangel et al.[10] The checklist consisted of 3 subscales containing 30 items in total. The 3 subscales were: 1. Potential Clinical Relevance, 2. Quality of Study Methodology, and 3. Quality of Discussion and Stated Conclusions. A maximum of 45 points could be scored. Scores ranging from 0 to 15 indicated a study of poor quality, studies scoring from 16 to 30 points were

considered to be fair and scores of 31 points or higher indicated a qualitatively good study. All studies of poor quality (scoring less than 16 points) were excluded.

Data extraction

Two reviewers (HV,IdB) used predefined criteria to extract the data from included publications. The predefined criteria concerned study design, population, and anorectal, urological, and gynecological function. Anorectal function was preferably scored according to the Krickenbeck criteria for postoperative results.[11] Furthermore, data on the use of bowel management, the presence of colostomies, and fecal incontinence were documented. Urological function was reported in terms of spontaneous voiding, need for intermittent catheterization, and the presence of a urinary diversion. Percentages of patients that were continent or incontinent for urine were also documented. Finally, gynecological function, including the presence of normal menstruations, percentages of patients who were sexually active, obstetric results were documented. In total, the reviewing process took 7 months, beginning in November 2011 and ending in June 2012.

Statistical analysis

Data were analyzed using SPSS (version 17; SPSS, Chicago, IL). Fisher's exact tests were used to compare anorectal, urological, and gynecological function parameters between centers with more experience (≥ 1 patients/year) and small centers (<1 patient/year).

Results

Study selection

The database searches resulted in 541 records from PubMed, 363 records from EMbase, and 302 records from Web of Science. After the removal of duplicates and triplicates 890 records were identified from the 3 databases. A total of 588 records were excluded based on the title alone. Subsequently, 289 records were excluded for not meeting the inclusion criteria after assessing the abstract (n=261) or the full text (n=28, Fig. 2.1). In the end, 13 studies met inclusion criteria and were used for qualitative synthesis. One study, scoring 7 out 45 points on the Rangel scale, was subsequently excluded.[2]

Study characteristics

The oldest publication included was from 1993 and 9 out of 12 studies used for final analysis were published after 2000. All of the included studies were retrospective chart reviews of the study centers' cloaca patient populations (Table 2.1). Included studies reported outcome on series ranging from 6 to 193 patients (median = 22), with a total of 340 patients taken into account that some studies report the same population in

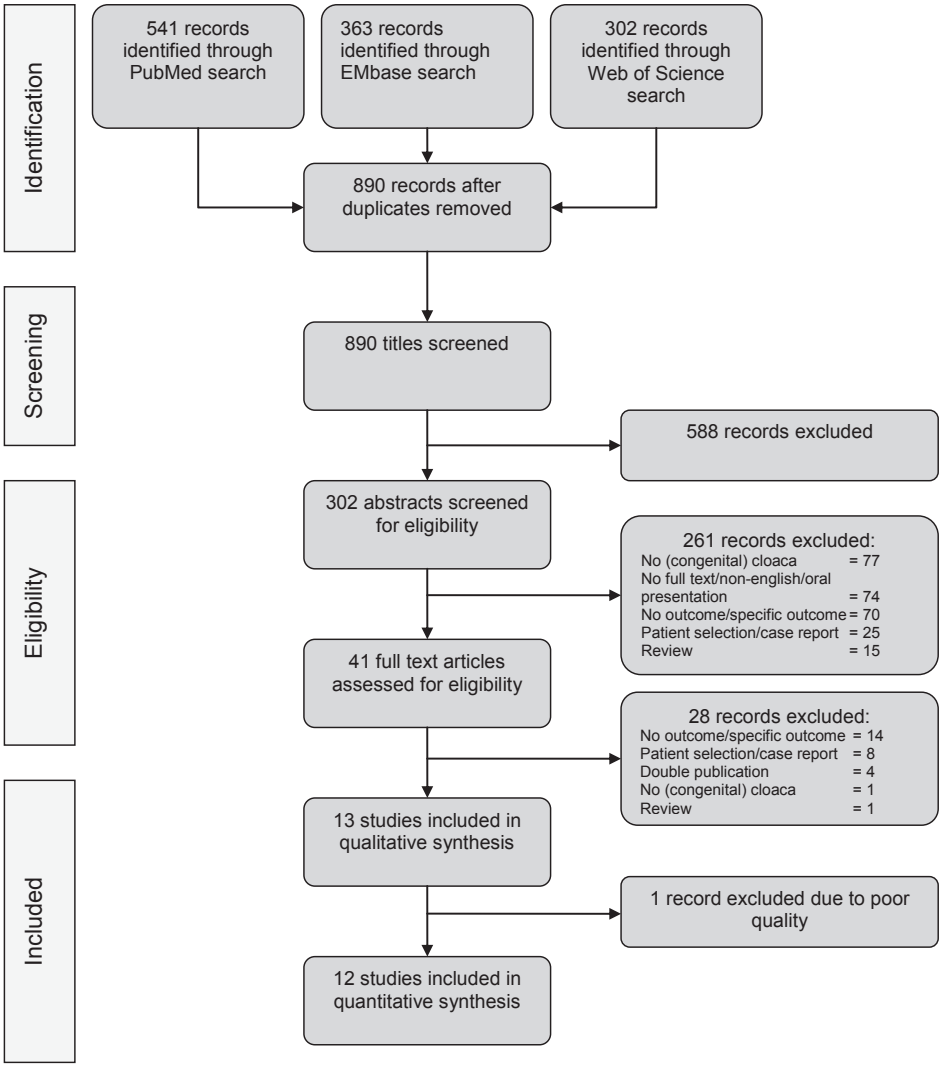

Figure 2.1 *Study selection flow chart*

separate publications. Eight studies (67%) presented solely patients with cloaca.[12-19] Two studies (17%) reported anorectal malformations (ARM) in general[20,21], and 2 (17%) compared patients with cloacal malformations to patients with other abnormalities (cloacal exstrophy in one, and urogenital sinus with congenital adrenal hyperplasia in the other).[22,23] Length of follow-up was reported in 9 studies and ranged from 5 months to 31.6 years. In only 6 of 12 studies was the status of the sacrum or spine defined. These associated anomalies have been found vital in predicting bowel and urinary functional results.[24,25] However, only 2 studies correlated sacral anatomy to functional outcome.[20,21]

Table 2.1 *Study characteristics.*

	Author	Country	Journal	Year	Number of Patients with CM	Quality[10]
1	Braga[12]	Canada	Canadian Urological Association Journal	2007	12	17
2	Camanni[22]	Italy	Journal of Urology	2009	6	23
3	Krstic[23]	Serbia	Pediatric Surgery International	2001	10	16
4	Kubota[13]	Japan	Pediatric Surgery International	2011	17	18
5	Leclair[14]	UK	Journal of Urology	2007	22	19
6	Levitt[15]	USA	Journal of Pediatric Surgery	1998	22	17
7	Peña[20]	USA	Seminars in Pediatric Surgery	1995	37	16
8	Peña[16]	USA	Journal of Pediatric Surgery	2004	193[a]	18
9	Rink[17]	USA	British Journal of Urology International	2005	22	16
10	Rintala[21]	Finland	Journal of Pediatric Surgery	1993	8	16
11	Warne[18]	UK	Journal of Urology	2002	50	16
12	Warne[19]	UK	Journal of Urology	2003	41	20

[a]*The study included 339 patients, however useful outcome was only available for 193 due to insufficient data in the other 146. CM = Cloacal malformations*

None of the studies correlated spinal anomalies such as tethered cord to urinary continence or need for intermittent catheterization. Mean study quality was 17.7 points (range 16-23). None of the included studies scored more than 30 points, the minimal score indicating good quality.[10]

Anorectal function

Seven of the 12 studies (58%) reported data on anorectal function for a total of 263 patients (Fig. 2.2A and 2.2B). According to the Krickenbeck criteria, voluntary bowel movements were reported in 108 of 188 patients (57%) in whom this factor was assessed. Soiling was documented in 146 of 205 patients (71%). However, reported in more than half the patients, constipation was only assessed in 61 patients, with 31 patients (51%) who suffered from constipation. Of the 245 patients with a cloacal malformation 81 (33%) suffered from fecal incontinence. Unfortunately, incontinence was reported without any further indication of severity. Only in the study of Peña *et al*. (2004) was fecal continence reported with 26 out 156 patients (17%) being totally continent. Seventeen of 58 patients (29%) used laxatives, 95 of 253 patients (38%) were on an enema program. Twelve (17%) of the 72 patients for whom this was reported ended up with a colostomy.

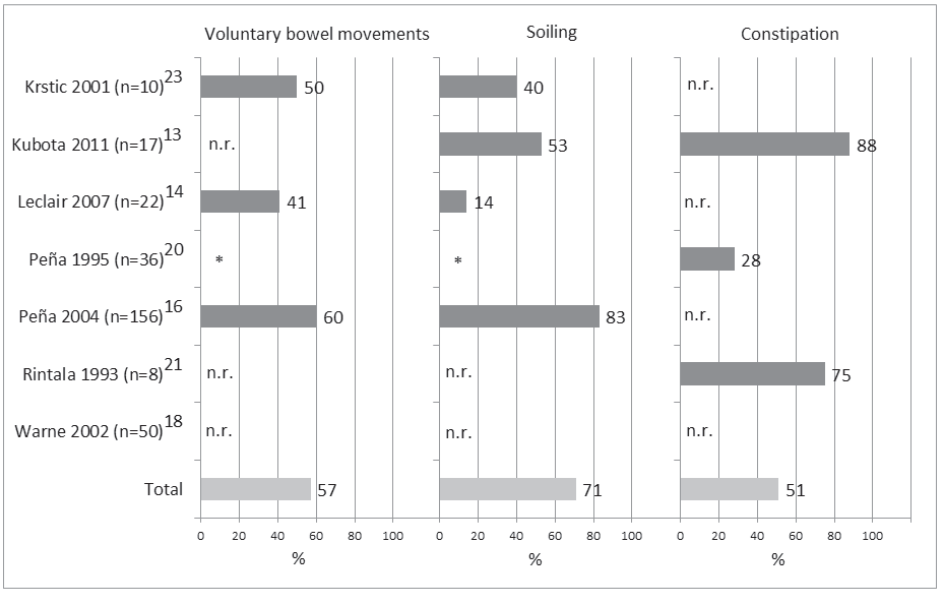

Figure 2.2A *Anorectal function according to the Krickenbeck classification.*
n.r. *not reported;* ******* *these criteria were reported in this study, but a larger study involving the same population[16] was used for review purposes.*

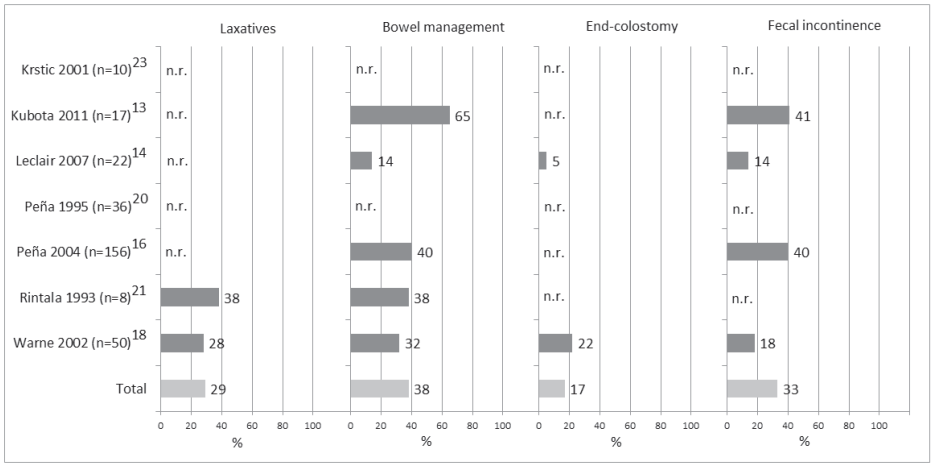

Figure 2.2B *Anorectal function according to non-Krickenbeck criteria.*
These signs and symptoms are not part of the Krickenbeck criteria but are of clinical importance to anorectal function and therefore often mentioned in the evaluation.
n.r. *not reported.*

Urological function

Nine studies (75%) reported urological function on a total of 332 separate patients (Fig. 2.3). Spontaneous voiding was assessed in 299 patients, of whom 138 (46%) were able

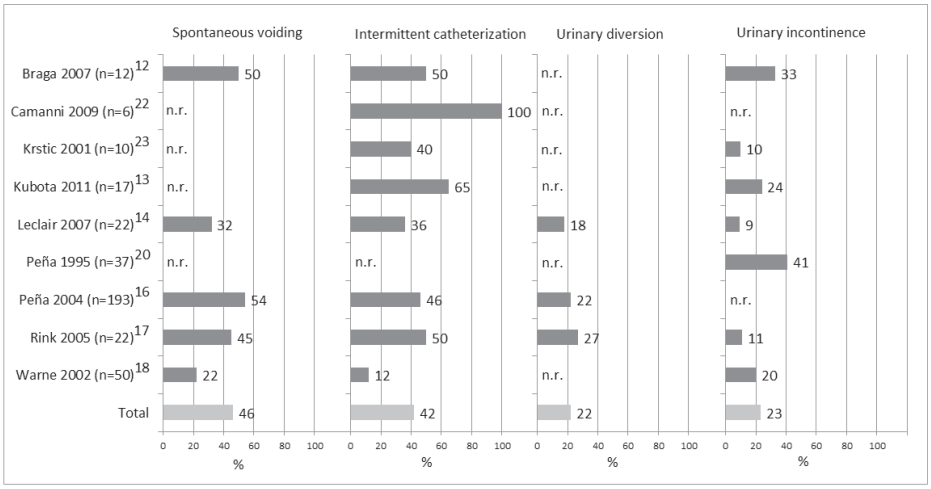

Figure 2.3 *Urological function.*
n.r. *not reported.*

to void spontaneously. Intermittent catheterization was reported in 141 of 332 patients (42%), 53 of 237 patients (22%) were reported to have a urinary diversion. In 166 patients the presence of urinary incontinence was assessed with 38 patients (23%) suffering from incontinence to some degree.

Gynecological function

Three studies (25%) reported on the outcome of gynecological function in a total of 71 patients (Fig. 2.4). Twenty-five of them (35%) had normal menstruations. Abnormal menstruations were noted in 6 of 49 patients (12%); early puberty and dysmenorrhea occurred in 3. Additional treatment was needed in 24 of 63 patients (38%) as a result of an obstructed menstruation causing hematometra. Twenty-five percent (16 of 63 patients) of the patients with a cloacal malformation had primary amenorrhea, consistent with the 1998 report in which Levitt *et al.* (1998) showed that only 2 patients with an amenorrhea had normal vaginas at birth; 3 (50%) had small, blind vaginas, 1 (17%) had no vagina. Only Warne *et al*. (2003) reported sexual activity in their patients, with 12 of 21 patients (57%) assessed have been sexually active.

Center size

Included studies reported outcome on series ranging from 6 to 193 patients (median = 22), with a total of 340 unique patients. In 9 studies more than 1 patient with a cloacal malformation was treated in that specific center per year.[13,14,16,18-21,23] None of the centers that treated less than 1 newborn patient with a cloaca per year reported anorectal or gynecological functions. This made comparison between experienced and less experi-

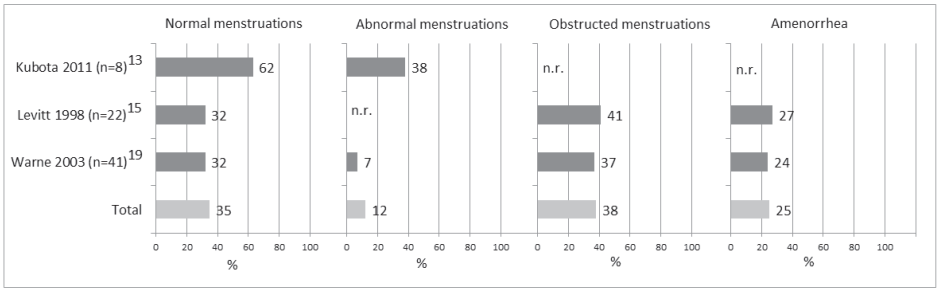

Figure 2.4 *Gynecological function.*
n.r. *not reported.*

Table 2.2 *Small versus large centers.*

	Center size				p-value
	n < 1/year		n ≥ 1/year		
Spontaneous voiding	16/34	(47%)	122/265	(46%)	1.000
CIC	23/40	(58%)	118/292	(40%)	0.060
Urinary diversion	6/22	(27%)	47/215	(22%)	0.593
Urinary incontinence	6/30	(20%)	32/136	(24%)	0.812

CIC = clean intermittent catheterization.

enced centers impossible for those items. Urological outcome was, however, properly reported in the less experienced centers (Table 2.2). Regarding urological function there was no difference between more experienced centers compared to the centers with limited experience.

Discussion

Cloacal malformations are complex congenital malformations that need multiple surgical interventions for definitive reconstruction. The aim of this review was to evaluate reported long-term functional outcome in patients with cloacal malformations. Twelve studies met all inclusion criteria and were eligible for quantitative analysis. For qualitative analysis we used a scale constructed by Rangel *et al.* (2003), which was especially created for retrospective observational studies in pediatric surgery, because pediatric surgical trials (prospective and randomized) are extremely difficult and rare.[10] Studies included in our review mainly reported case series and did not rely on a comparison with a control group. Therefore, scores on the Rangel scale are by definition lower than when using the scale for comparative studies. None of the studies scored good quality which unfortunately weakens the overall strength of our conclusions.

The surgical reconstruction of cloacal malformations has three goals: to achieve adequate anorectal function, urological function, and gynecological or sexual function. Only one of the studies we reviewed reported outcome in all 3 functional systems[13], although 2 centers did report all 3 functions of their patients in separate publications.[15,16,18-20] Five studies reported outcomes in 2 systems[14,16,18,20,23] and 6 reported outcome in 1 system only.[12,15,17,19,21,22]

Cumulatively, in terms of anorectal function only 57% of all patients with a cloaca had voluntary bowel movements. Both soiling (71%) and constipation (51%) are frequently seen disturbances. Only 17% of the patients were fully continent for feces. Urological outcome is comparably impaired with less than half of the patients being able to void spontaneously. It is known that both colorectal and urological outcome are correlated with sacral anatomy and spinal anomalies.[25] None of the studies correlated spinal anomalies such as tethered cord to urinary continence or need for intermittent catheterization. Since sacral anatomy and spinal anomalies are factors that predict functional outcome these items should be reported for every patient and should be correlated to functional outcome.

Gynecological outcome was reported in only 3 studies, which shows that this is still an overlooked problem in the reporting of long-term outcome in patients with cloacal malformations. Only 35% of the patients that reached the age of puberty presented with normal menstruation; a thorough and standardized gynecological work-up should be mandatory in all patients with cloacal malformations 6-9 months after the beginning of puberty (thelarche).[26] More than half of the patients in whom this was assessed were sexually active. However, items such as sexual satisfaction and obstetric abilities are not reported and would be a point of interest in future studies.

The studies in this review all used different ways of reporting outcome. Regarding literature for anorectal outcome in particular several modes of reporting functional outcome have been presented.[11,27-29] Most studies report their own system of criteria involved in anorectal function. In general, we were able to deduct these outcome parameters to the Krickenbeck classification for postoperative results.[11] However, some important details such as the presence of an end-colostomy, are not accounted for in the Krickenbeck classification. Yet, 17% of all patients ended up with a colostomy. Therefore, the Krickenbeck classification may need some adjustments. Other studies that did not meet inclusion criteria used numerical scoring systems to report anorectal function.[30,31] These results are even more difficult to interpret because the exact cause of any impairment is not retrievable and thus comparison of outcomes are almost impossible. We suggest an adjusted Krickenbeck classification with regard to the use of enema programs and

Table 2.3 *Suggestions for reporting of functional outcome in patients with cloacal malformation.*

Age 0 (newborn)	Length of common channel
	Urological anatomy *Kidney and bladder abnormalities*
	Gynecological anatomy *Hydrocolpos, double system, vaginal agenesis*
	Sacral & spinal anatomy Sacral ratio
Age 3-5 (potty training)	Colorectal function *VBM, soiling, constipation, bowel management, colostomy*
	Urological function *Spontaneous voiding, CIC, diversion, incontinence, kidney function*
Age 12-15 (puberty)	Colorectal function (see age 3-5)
	Urological function (see age 3-5)
	Gynecological function *Menstrual status*
Age 16-25 (adulthood)	Colorectal function (see age 3-5)
	Urological function (see age 3-5)
	Gynecological function *Menstrual status, sexual function, pregnancy, obstetric ability*

Key issues to be evaluated and documented in patients with cloacal malformation at different ages. These issues are to be evaluated besides the normal evaluation and screening of newborns with anorectal malformation, e.g. the VACTERL screening.
VBM = Voluntary bowel movements; CIC = Clean intermittent catheterization.

presence of colostomies as the best option to measure anorectal functional outcome. A more extensive classification, like the Rintala score, describes the dysfunction more adequately, but is cumbersome and needs general usage and validation before it can be deemed valuable.[27]

For both urological and gynecological function, no predefined classifications were used, but rather several different outcome criteria were reported. Although these outcome criteria might be obvious to report, the use of one predefined classification may increase uniform reporting in these functional systems and need to be developed and evaluated (table 2.3).

To see whether more experienced centers have a better outcome in these patients, we compared studies with less than 1 patient with a cloacal malformation treated per year with the ones having more than 1 patient per year. Our data suggest that centers with limited experience report similar results as centers with more experience. However, we found only 1 center that treats more than 5 patients per year in all studies included in this review. This indicates limited experience worldwide with poor centralization of

complex surgical care. Although this review does not show big differences between small and larger centers, more experienced surgeons and institutions are more likely able to deliver high quality medical treatment and specialized care for patients suffering from rare conditions, such as cloacal malformations.

In conclusion, with this systematic review we present the reported functional outcome of the largest pooled cohort of patients with cloacal malformations. The review shows that functional disturbances are still frequently encountered in all three functional systems. Better reporting of functional outcome in patients with cloacal malformations should increase knowledge about long-term results in patients with this rare malformation and allow for a higher quality study. An international registration and perhaps a new Krickenbeck meeting is needed to get more knowledge and consensus about these difficult patients. Specialized care centers with a multi-disciplinary approach may be of great importance for patients with these rare and complex conditions.

References

1. Kluth D, Fiegel HC, Metzger R. Embryology of the hindgut. Semin Pediatr Surg 2011; 20: 152-160.
2. Hendren WH. Cloaca, the most severe degree of imperforate anus: experience with 195 cases. Ann Surg 1998; 228: 331-346.
3. Warne SA, Hiorns MP, Curry J et al. Understanding cloacal anomalies. Arch Dis Child 2011; 96: 1072-1076.
4. Pena A, deVries PA. Posterior sagittal anorectoplasty: important technical considerations and new applications. J Pediatr Surg 1982; 17: 796-811.
5. deVries PA, Pena A. Posterior sagittal anorectoplasty. J Pediatr Surg 1982; 17: 638-643.
6. Pena A. Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997; 32: 263-267.
7. Lahoti BK, Aggarwal G, Satsangi B et al. Total urogenital sinus mobilization in common cloaca: experience of 25 cases. J Pediatr Urol 2011; 7: 219-223.
8. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
9. Moher D, Liberati A, Tetzlaff et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339: b2535.
10. Rangel SJ, Kelsey J, Colby CE et al. Development of a quality assessment scale for retrospective clinical studies in pediatric surgery. J Pediatr Surg 2003; 38: 390-396.
11. Holschneider A, Hutson J, Peña A et al. Preliminary report on the International Conference for the Development of Standards for the Treatment of Anorectal Malformations. J Pediatr Surg 2005; 40: 1521-1526.
12. Braga LH, Lorenzo AJ, Dave S et al. Long-term renal function and continence status in patients with cloacal malformation. Can Urol Assoc J 2007; 1: 371-376.
13. Kubota A, Nara K, Kawahara H et al. Therapeutic strategy for persistent cloaca: the efficacy of antegrade continent enema as a salvage surgery. Pediatr Surg Int 2011; 27: 505-508.
14. Leclair MD, Gundetti M, Kiely EM et al: The surgical outcome of total urogenital mobilization for cloacal repair. J Urol 2007; 177: 1492-1495.
15. Levitt MA, Stein DM, Pena A. Gynecologic concerns in the treatment of teenagers with cloaca. J Pediatr Surg 1998; 33: 188-193.
16. Pena A, Levitt MA, Hong A et al. Surgical management of cloacal malformations: a review of 339 patients. J Pediatr Surg 2004; 39: 470-479.
17. Rink RC, Herndon CD, Cain MP et al. Upper and lower urinary tract outcome after surgical repair of cloacal malformations: a three-decade experience. BJU Int 2005; 96: 131-134.
18. Warne SA, Wilcox DT, Ransley PG. Long-term urological outcome of patients presenting with persistent cloaca. J Urol 2002; 168: 1859-1862.
19. Warne SA, Wilcox DT, Creighton S et al. Long-term gynecological outcome of patients with persistent cloaca. J Urol 2003; 170: 1493-1496.
20. Pena A. Anorectal malformations. Semin Pediatr Surg 1995; 4: 35-47.

21. Rintala R, Lindahl H, Marttinen E et al. Constipation is a major functional complication after internal sphincter-saving posterior sagittal anorectoplasty for high and intermediate anorectal malformations. J Pediatr Surg 1993; 28: 1054-1058.

22. Camanni D, Zaccara A, Capitanucci ML et al. Bladder after total urogenital mobilization for congenital adrenal hyperplasia and cloaca--does it behave the same? J Urol 2009; 182: 1892-1897.

23. Krstic ZD, Lukac M, Lukac R et al. Surgical treatment of cloacal anomalies. Pediatr Surg Int 2001; 17: 329-333.

24. Levitt MA, Pena A. Outcomes from the correction of anorectal malformations. Curr Opin Pediatr 2005; 17: 394-401.

25. Levitt MA, Pena A. Anorectal malformations. Orphanet J Rare Dis 2007; 2: 33.

26. Breech L. Gynecologic concerns in patients with anorectal malformations. Semin Pediatr Surg 2010; 19: 139-145.

27. Rintala RJ, Lindahl H. Is normal bowel function possible after repair of intermediate and high anorectal malformations? J Pediatr Surg 1995; 30: 491-494.

28. Ochi T, Okazaki T, Miyano G et al. A comparison of clinical protocols for assessing postoperative fecal continence in anorectal malformation. Pediatr Surg Int 2012; 28: 1-4.

29. Holschneider AM, Jesch NK, Stragholz E et al. Surgical methods for anorectal malformations from Rehbein to Pena--critical assessment of score systems and proposal for a new classification. Eur J Pediatr Surg 2002; 12: 73-82.

30. Kaselas C, Philippopoulos A, Petropoulos A. Evaluation of long-term functional outcomes after surgical treatment of anorectal malformations. Int J Colorectal Dis 2011; 26: 351-356.

31. Hashish MS, Dawoud HH, Hirschl RB et al. Long-term functional outcome and quality of life in patients with high imperforate anus. J Pediatr Surg 2010; 45: 224-230.

Chapter 3

Early versus late reconstruction of cloacal malformations; the effects on postoperative complications and long-term colorectal outcome.

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Abstract

Introduction Patients with a cloacal malformation generally undergo reconstructive surgery within the first years of life. However, the ideal age for surgery has rarely been mentioned. Aim of this study was to report differences in outcome between early (<6 months) and late repair of cloacal malformations.

Methods Charts of patients with a cloacal malformation treated in 5 pediatric surgical centers between 1985 and 2009 were retrospectively studied for associated anomalies, postoperative complications, and colorectal and urological outcome.

Results Forty-two patients were eligible for this study, giving a mean exposure of less than 1 patient yearly per center. Forty-five percent of the patients had a short common channel (>3cm) and 14% had a long common channel; length of common channel was missing in 41 % of the patients. Median age of the cloacal reconstruction was 9 months (range 1-121 months). Twelve patients (29%) underwent an early surgical repair (within the first 6 months of age; median 3 months); 30 (71%) patients underwent a late repair (after 6 months of age; median 14 months). Eighteen postoperative complications (<30 days) had been documented in 15 patients (35%), with significant more perineal wound dehiscences in patients with an early repair (42% vs. 10%, p=0.031). There were no differences in complication rate between patients with short and long common channels. Mean follow-up was 142 months (range 15-289). At the last follow-up 10 patients (24%) had voluntary bowel movements. Fourteen patients (33%) had complaints of soiling, 25 (60%) were constipated, with no differences between the early and late repair groups. Urological outcome was similar in both groups.

Conclusions Postoperative complications are common in patients with cloacal malformations. Early repair can give more wound dehiscences, however, without affecting long-term functional outcome. All centers had limited annual exposure of less than 1 patient. In these clinical settings ideal age of cloacal reconstruction seems to be between 6 and 12 months. In general, centralized care for these complex malformations may be the crucial factor for less postoperative complications and better long-term outcome.

Introduction

The most complex anorectal malformation in females is a cloacal malformation, in which the rectum, vagina, and urethra drain into a common channel.[1] The most commonly used surgical approach to reconstruct a cloaca is a posterior sagittal anorectoplasty (PSARP), extended with either a posterior sagittal anorecto vagino urethroplasty (PSARVUP), or the total urogenital mobilization (TUM).[2,3] Mobilization of the rectum by laparotomy or laparoscopy may be necessary depending on the length of the common channel. The aim of surgery is to achieve best possible colorectal, urological, and gynecological function. In the largest study by *Peña et al.* presenting outcome of patients with cloacal malformations, the patients are operated on between the first and 12th month of age.[4] However, when born within their institution and with an uncomplicated course, the authors prefer to operate earlier, even after 1 month of age. The optimal age for cloacal reconstruction, however, has not been studied, particularly not in centers with less exposure to these patients. Aim of this study was to evaluate differences in postoperative complications and long-term outcome between patients who underwent early reconstruction of the cloaca versus late reconstruction.

Patients and methods

Medical records of all 55 patients with a cloacal malformation treated between January of 1985 and December of 2009 in five pediatric surgical centers in the Netherlands were retrospectively reviewed. Each center employs between 5 and 7 pediatric surgeons of whom 1 or 2 are experienced in conducting reconstructive surgery for cloacal malformations. Only patients born after the introduction of the posterior sagittal approach in the Netherlands (1985) were included. Furthermore, patients born after 2009 were excluded because continence was not assessable in them due to young age. Cloacal malformations were classified as having a short common channel (less than 3.0 cm) or a long common channel (more than 3.0 cm).[5] For this study we recorded information regarding associated anomalies, type of surgery, postoperative complications and long-term outcome. Long-term outcome was defined as colorectal function assessed according to the Krickenbeck classification (Table 3.1), use of a bowel management program, and the presence of a colostomy. Also urological function, e.g. the need for clean intermittent bladder catheterization and the ability to void spontaneously, was recorded, but is more extensively reported separately. For analysis patients were divided in two groups: one with patients who underwent early reconstruction of the cloaca (0-6 months of age) and one with patients who underwent late reconstruction (after more than 6 months of age). Groups were compared using Fishers' exact test in SPSS 17.

Table 3.1 *Krickenbeck classification for postoperative results*[5]

International classification (Krickenbeck) for postoperative results	
1. Voluntary bowel movements	Yes/No
Feeling of urge,	
Capacity to verbalize,	
Hold the bowel movement	
2. Soiling	Yes/No
Grade 1	Occasionally (once or twice per week)
Grade 2	Every day, no social problem
Grade 3	Constant, social problem
3. Constipation	Yes/No
Grade 1	Manageable by changes in diet
Grade 2	Requires laxatives
Grade 3	Resistant to laxatives

Results

From a total of 55 patients 12 were subsequently excluded for lack of good data on functional outcome. One patient died of a clear cell sarcoma of the kidney at age 10 without having undergone cloacal repair; she was excluded. Thus, final analysis included 42 patients. Median age of the cloacal reconstruction was 9 months (range 1-121 months). Twelve patients (29%) were operated on within the first 6 months of age (median 3 months, range 1-6); 30 patients (71%) underwent surgery more than 6 months after birth (median 14 months, range 7-121).

Mean length of the common channel was 2.2 cm (range 1.0-4.0 cm). Nineteen patients (45%) had a common channel shorter than 3.0 cm (Table 3.2); 6 patients (14%) had a long (more than 3.0 cm) common channel. Information about length of common channel was missing in 17 cases (41%). Associated anomalies were documented in 37 (88%) of the 42 patients. An abnormal sacrum was seen in 22 patients (52%); 7 patients (17%) suffered from spinal dysraphism. A duplicature of the Müllerian system was seen in 27 patients (64%); agenesis of the Müllerian structures was present in 4 patients (10%). In general, anomalies of the Müllerian structures were seen more often in patients operated after more than 6 months of age (50% vs. 83%, p=0.049). In 24 patients (57%) a PSARVUP was done, in 18 patients (43%) the PSARP was combined with a TUM. In 10 cases (24%) the surgical reconstruction was combined with a laparotomy. Eighteen complications within the first 30 days after the cloacal reconstruction were seen in 15 patients (36%); 7 patients (58%) in the early repair group and 8 (27%) in the group of late repair (p=0.078, Table 3.3). Perineal wound dehiscences were seen significantly more frequent in the early repair

Table 3.2 *Patient characteristics and type of surgery.*

	Early (n=12)		Late (n=30)		Total (n=42)		p-value
	n	%	n	%	n	%	
Short common channel	8	67	11	37	19	45	0.129
Long common channel	0	0	6	20	6	14	
Length missing	4	33	13	43	17	41	0.731
Associated anomalies	9	75	28	93	37	88	0.131
Sacral anomalies	5	42	17	57	22	52	0.499
Spinal anomalies	2	17	5	17	7	17	1.000
Müllerian anomalies	6	50	25	83	31	74	*0.049*
Duplicature	6	50	21	70	27	64	0.292
Agenesis	0	0	4	13	4	10	0.308
PSARVUP	6	50	18	60	24	57	0.732
TUM	6	50	12	40	18	43	
Laparotomy assisted	1	8	9	30	10	24	0.233

PSARVUP Posterior sagittal anorecto vagino urethroplasty; TUM Total urogenital mobilization

Table 3.3 *Postoperative complications (<30days after surgery).*

	Early repair (n=12)		Late repair (n=30)		Total (n=42)		p-value
	n	%	n	%	n	%	
Complications	7	58	8	27	15*	36	0.078
Perineal wound dehiscence	5	42	3	10	8	19	*0.031*
Recurrent fistula	1	8	6	20	7	17	0.651
Rectal prolapse	1	8	0	0	1	2	0.286
UTI	1	8	0	0	1	2	0.286
fever (unknown cause)	1	8	0	0	1	2	0.286
Vaginal complications (stricture, prolapse)	0	0	0	0	0	0	-

UTI Urinary tract infection

** Number of patients, with a total of 18 complications.*

group (42% vs. 10%, p=0.031). Recurrent fistulas were seen once (8%) in the early repair group and 6 times (20%) in the late repair group, however, this difference was not significant (p=0.651). No vaginal complications were seen within 30 days of the surgical repair, although 9 patients needed a secondary vaginoplasty at a later stage due to severe vaginal stricture. Complication rate was regardless of the presence of sacral or spinal anomalies (Table 3.4A) and, remarkably, there was no difference in complications between patients with short common channels and the patients with long common channels (Table 3.4B).

Median follow-up was 142 months (range 15-289). Regarding functional outcome voluntary bowel movements (VBM) were seen in 10 patients (24%), with no difference

Table 3.4A *Spinal and sacral anomalies related to complications and outcome.*

	Spinal/sacral anomalies				p-value
	Yes (n=23)		No (n=19)		
	n	%	n	%	
Complications	7	30	8	42	0.525
Dehiscence	4	17	4	21	1.000
VBM	4	17	6	32	0.468
Soiling	6	26	8	42	0.335
Constipation	14	61	11	58	1.000
CIC	8	35	6	32	1.000
SV	12	52	17	89	*0.017*

VBM Voluntary Bowel Movements; CIC Clean intermittent catheterization; SV Spontaneous voiding.

Table 3.4B *Length of common channel related to complications and outcome.*

	Common channel				p-value
	SCC (n=19)		LCC (n=6)		
	n	%	N	%	
Complications	5	26	2	33	1.000
Dehiscence	3	16	0	0	0.554
VBM	7	37	0	0	0.137
Soiling	7	37	0	0	0.137
Constipation	9	47	5	83	0.180
CIC	4	21	3	50	0.299
SV	16	84	2	33	*0.032*

VBM Voluntary Bowel Movements; CIC Clean intermittent catheterization; SV Spontaneous voiding; SCC Short common channel, <3cm; LCC Long common channel, >3cm.

between groups of early repair and late repair (25% vs. 23%, p=1.000, Table 3.5). Soiling was seen 33% in both the early and late repair groups. Constipation was reported in 60% of the patients with no difference between both groups. Bowel management was needed in 67% of the patients in both the early repair group and the late repair group. An end-colostomy was created in 4 patients (10%) due to recurrent anal stenosis. Seven patients (37%) with a short common channel had VBM, whereas none of the patients with a long common channel had VBM (Table 3.4B). However, this was not significantly different. Furthermore, there were no significant differences between these groups regarding other items for colorectal outcome (constipation, soiling).

Regarding urological outcome 14 patients (33%) needed clean intermittent catheterization, with no difference between groups of early and late repair (Table 3.5). Spontaneous voiding rates were similar for patients who underwent early (83%), and late (63%) repair (p = 0.282). Patients without spinal or sacral anomalies were more frequently able to

Table 3.5 *Colorectal and urological outcome*

	Early repair (n=12)		Late repair (n=30)		Total (n=42)		p-value
	n	%	n	%	n	%	
VBM	3	25	7	23	10	24	1.000
Soiling	4	33	10	33	14	33	1.000
Grade 1	2	17	2	7	4	9	0.565
Grade 2	1	8	4	13	5	12	1.000
Grade 3	1	8	4	13	5	12	1.000
Constipation	9	75	16	53	25	60	0.300
Grade 1	0	-	0	-	0	-	-
Grade 2	2	17	1	3	3	7	0.192
Grade 3	7	58	15	50	22	53	0.739
Bowel management	8	67	20	67	28	67	1.000
Colostomy	1	8	3	10	4	10	1.000
CIC	3	25	11	37	14	33	0.719
Spontaneous voiding	10	83	19	63	29	69	0.282

VBM Voluntary Bowel Movements; CIC Clean intermittent catheterization.

void spontaneously (89% vs. 52%, p=0.017, Table 3.4A). Regarding length of common channel 84% of the patients with a short common channel were able to void spontaneously compared to 33% (p=0.032, Table 3.4B) of patients with a long common channel.

Discussion

From 1982 results for the repair of anorectal malformations improved with the introduction of the posterior sagittal approach.[6] The aim of this study was to compare outcome after early and late repair of cloacal malformations. The median age of the patients at reconstructive surgery was 9 months in our series. Peña and Levitt perform their surgery within the first 12 months of life.[4] However, when patients are born within their institution the reconstruction is done when the baby is 1 month of age. Other studies presented series of patients with cloacal malformations that were operated between the second month and 5 years of age, with means ranging from 9 months to 20 months.[7-9] Age of cloacal reconstruction thus has a wide range and little is mentioned regarding the ideal age for surgery. This study is the first in literature ever comparing early and late cloacal malformation repair.

Müllerian anomalies were more frequent reported for patients who underwent a late cloacal repair. Older infants may have been better and more easily inspected before and

during surgery, otherwise it may be true that both groups were less comparable due to the retrospective character of the study without any randomization. However, for other anatomical factors, such as length of common channel, or the presence of sacral and spinal anomalies, we did not find any differences between the two groups.

Postoperative complications were common in our patients with cloacal malformations (35%). This is more than reported in other studies with complications rates of 9-23%.[8,10,11] Unexpectedly, we did not see significant differences between the patients with short and long common channels, although this may be due to small patient groups (type II error). We did, however, find significantly more perineal wound dehiscences in the early repair group (42%) than in the late repair group (10%). Wound healing can be impaired as a consequence of malnutrition, edema, or physiological instability.[12] However, these matters were never recorded in any of our cases. Therefore, surgical experience, or the lack of that, may play a more important role in this.[13] Surgical techniques for cloacal may be more challenging in small newborns compared to infants of 9 months when performed by less experienced surgeons. On the other hand, it is generally known that younger patients may have more easily mobilized structures and shorter distances to reach the perineum, which is an argument for earlier repair. We furthermore observed a high rate of recurrent fistula. However, this was not significantly different between short and long common channels or early and late repair groups. Therefore, regarding postoperative complications our data suggest that cloacal reconstruction is best conducted after the first six months of life in centers with limited experience. Centralization of care for these rare malformations is probably the most important factor to reduce the number of postoperative complications and could also make it feasible to perform early reconstructions as suggested by others.[4,10]

In general, patients with cloacal malformation present with severe functional disturbances on the long-term. In our series only 24% of the patients achieved voluntary bowel movements. Although we observed a better outcome in patients with short common channels (37%), others reported voluntary bowel movements up to 50% of their cloaca patients.[10] Regardless of experience, colorectal outcome is always much worse compared to patients with less complex anorectal malformations, e.g. patients with vestibular fistulas which have been reported to achieve voluntary bowel movements up to 92%.[14]

The differences in postoperative complications between the early repair group and the late repair group did not have any effect on long-term colorectal outcome. The percentages of patients with voluntary bowel movements, soiling, and constipation were similar in both groups. In terms of urological outcome, no differences between groups were

seen for spontaneous voiding or the need for CIC. Overall, it must be taken into account that the late repair group contained more patients with short common channels than the early repair group. This may have influenced outcome in these patients.

The major limitation of our study is its retrospective nature. Missing data were encountered in several of the patient files and especially minor postoperative complications might have gone by undocumented. Since the Krickenbeck criteria were published in 2005, older cases could not have been followed up according to these criteria. In these cases the case notes in patient files were computed into Krickenbeck criteria outcomes. Although our study concerns the second largest series of its kind it is still limited by a small sample size. These matters may influence study reliability, therefore, all future patients of several of the participating centers in this study will be included in a European network for patients with anorectal malformations (ARM-net) and will have prospective follow-up.[15]

Conclusion

The repair of cloacal malformations is still a surgical challenge. All centers had limited exposure of cloaca patients. Postoperative complications were common in these patients when operated on within the first 6 months of age, i.e. more wound dehiscences. Fortunately, this difference on the short-term does not reflect on the long-term functional outcome. Although patient groups are small, it seems that ideal age of cloacal reconstruction may be between 6 and 12 months of age in centers with limited experience. Centralized care centers and an increased experience might lead to better results in the complex group of patients.

References

1. Hendren WH. Cloaca, the most severe degree of imperforate anus: experience with 195 cases. Ann Surg 1998; 228: 331-346.
2. Pena A. Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997; 32: 263-267.
3. Pena A, Levitt MA. Surgical management of cloacal malformations. Semin Neonatol 2003; 8: 249-57.
4. Pena A, Levitt MA, Hong A et al. Surgical management of cloacal malformations: a review of 339 patients. J Pediatr Surg 2004; 39: 470-479.
5. Holschneider A, Hutson J, Peña A et al. Preliminary report on the International Conference for the Development of Standards for the Treatment of Anorectal Malformations. J Pediatr Surg 2005; 40: 1521-1526.
6. Holschneider AM, Jesch NK, Stragholz E et al. Surgical methods for anorectal malformations from Rehbein to Pena--critical assessment of score systems and proposal for a new classification. Eur J Pediatr Surg 2002; 12: 73-82.
7. Kubota A, Nara K, Kawahara H et al. Therapeutic strategy for persistent cloaca: the efficacy of antegrade continent enema as a salvage surgery. Pediatr Surg Int 2011; 27: 505-508.
8. Leclair MD, Gundetti M, Kiely EM et al. The surgical outcome of total urogenital mobilization for cloacal repair. J Urol 2007; 177: 1492-1495.
9. Braga LH, Lorenzo AJ, Dave S et al. Long-term renal function and continence status in patients with cloacal malformation. Can Urol Assoc J 2007; 1: 371-376.
10. Levitt MA, Pena A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg 2010; 19: 128-138.
11. Matsui F, Shimada K, Matsumoto F et al. Bladder function after total urogenital mobilization for persistent cloaca. J Urol 2009; 182: 2455-2459.
12. Baharestani MM. An overview of neonatal and pediatric wound care knowledge and considerations. Ostomy Wound Manage 2007; 53: 34-36.
13. Levitt MA, Bischoff A, Pena A. Pitfalls and challenges of cloaca repair: how to reduce the need for reoperations. J Pediatr Surg 2011; 46: 1250-1255.
14. Levitt MA, Pena A. Outcomes from the correction of anorectal malformations. Curr Opin Pediatr 2005; 17: 394-401.
15. de Blaauw, Weijers CHW, Schmiedeke E et al. First results of a European multi-center registry of patients with anorectal malformations. J Pediatr Surg 2013; 48: 2530-2535.

Chapter 4

Urogenital function after cloacal reconstruction, two techniques evaluated.

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Abstract

Objective Current surgical techniques for cloacal reconstruction are posterior sagittal anorecto vagino urethroplasty (PSARVUP) and posterior sagittal anorectoplasty (PSARP) with total urogenital mobilization (TUM). Aim of this study was to explore the results of reconstructive cloaca surgery in the Netherlands and evaluate urogenital function after PSARVUP and TUM.

Patients and methods Medical records of 5 pediatric surgical departments in the Netherlands were studied for patients with cloacal malformations treated between 1985 and 2009. Forty-two patients were eligible and patients with short common channels were categorized in PSARVUP and TUM groups. Groups were compared using Fisher's exact test.

Results Median age at time of surgery was 9 months (range 1-121). In 24 patients (57%) a PSARVUP was done, in 18 patients (43%) TUM. Median follow-up was 142 months (range 15-289). At follow-up spontaneous voiding was seen in 29 patients (69%). Clean intermittent catheterization (CIC) was needed in 14 patients (33%); a urinary diversion was created in 10 patients (24%). In total 32 patients (76%) were dry with no involuntary loss of urine per urethra. Recurrent urinary tract infections were seen in 23 patients (55%). When comparing PSARVUP and TUM groups in our series of patients with short common channels, there were no differences in urological outcome. Normal menstruation was present in 11 of the 20 patients who reached puberty (55%).

Conclusion Urogenital functional outcome after reconstructive surgery for cloacal malformations was similar in PSARVUP and TUM groups in patients with short common channels. A thorough urological follow-up is needed to establish the long-term bladder function and urinary incontinence results to prevent long-term risks of recurrent UTI. Albeit without differences between PSARVUP and TUM groups, 45% of the patients present with abnormal or absent menstruations. Gynecological follow-up is mandatory in all patients with cloacal malformations 6 months after the first sign of puberty.

Introduction

In females the most complex anorectal malformation is a cloacal malformation, in which the rectum, vagina, and urethra drain into one common channel.[1] Current approach for surgical correction of the cloaca is based on the posterior sagittal approach as proposed by Peña in 1982.[2] This technique was then modified to the posterior sagittal anorecto vagino urethroplasty (PSARVUP) for cloacal malformations in particular.[3] In 1997 the total urogenital mobilization (TUM) was introduced as a novel technique for the reconstruction of cloacas, leading to decreased operation time and improved cosmetic results.[4] Currently, TUM is first choice of surgery in many clinics, particularly in patients with cloacas with limited length of common channel (less than 3 cm).[5] Patients with short common channel cloacas generally have better long-term functional outcome than patients with long common channels.[5] However, it is suggested that extensive mobilization of the urethra, bladder neck, and vagina in the TUM operation may lead to impaired urogenital function.[6-8] To date reports of large cohorts comparing PSARVUP to TUM have not been published. With this study we reviewed the patients with cloacal malformations of the past 25 years in the major pediatric surgical centers in the Netherlands. Patients with short common channels who underwent TUM were compared to patients who were operated on by PSARVUP. Aim of the study was to describe and assess the risk of long-term urogenital disturbances as a consequence of TUM and PSARVUP surgeries.

Materials and methods

Medical records of 5 pediatric surgical departments in the Netherlands were studied for patients with a cloacal malformation treated between 1985 and 2009. Fifty-five patients were identified, of whom 13 (5 TUM, 4 PSARVUP, 4 missing data regarding surgical approach) were subsequently excluded due to young age or lack of completeness of the data. All patients with a cloacal malformation had a structured work-up including a cardiac and renal ultrasound, voiding cysto-urethrogram or urodynamic study, sacral X-ray and spinal ultrasound according to the national consensus in the Netherlands. After approval from the institutions' ethical committee, medical records were reviewed for information including associated anomalies, surgical approaches, complications, and functional outcome at latest follow-up. Surgical approaches were either posterior sagittal anorecto vagino urethroplasty (PSARVUP), in which the urogenital sinus is separated in vaginal or urethral tissue, or posterior sagittal anorectoplasty (PSARP) with total urogenital mobilization (TUM), in which the urogenital sinus is mobilized *en bloc* to reach the perineum.[2,4] Since this study was a retrospective analysis, choice of surgical

technique mainly depended on patient details (length of common channel as measured during preoperative cystoscopy), preference of the surgeon, and for older cases: lack of other available techniques. Surgical complications and colorectal outcome were reported elsewhere.[9] In this study urological and gynecological aspects are reported. The outcome criteria for urological function were: spontaneous voiding, need for intermittent catheterization, presence of a urinary diversion, urinary incontinence (urethral loss of urine), recurrent urinary tract infections (UTI), and need for kidney transplantations. Urinary diversions were either a continent diversion with a catheterizable Mitrofanoff channel or an incontinent vesicostomy. Recurrent urinary tract infections were defined as more than 3 infections per year. Menstrual status and pregnancies served as outcome measures for gynecological function in the patients who reached puberty. Since both PSARVUP as well as TUM were widely used in the patients with short common channels outcome after each type of surgery was compared for this group of patients using Fishers' exact test for group comparison.

Results

Forty-two charts were included for this review. Information regarding length of common channel was retrievable from the medical chart in 25 patients (59%). Mean length of the common channel was 2.2 cm (range 1.0-4.0 cm). Nineteen patients had a common channel shorter than 3.0 cm, 6 had a long (at least 3.0 cm) common channel (Table 4.1). Associated anomalies had been documented in 37 (88%) of the 42 patients. Sacral and spinal anomalies are predictors for worse urological outcome; an abnormal sacrum was seen in 22 patients (52%); 7 patients (17%) suffered from spinal dysraphism. Kidney abnormalities were seen in 21 patients (50%). A duplicature of the Müllerian system was seen in 27 patients (64%); agenesis of the Müllerian structures was present in 4 patients (10%).
Median age at time of the cloacal reconstruction was 9 months (range 1-121 months). In 24 of 42 patients (57%) a PSARVUP was done, in the other 18 (43%) the PSARP was combined with a TUM. In 10 cases (24%) the surgical reconstruction was combined with a laparotomy.

Median follow-up was 142 months (range 15-289). After surgery spontaneous voiding was seen in 29 patients (69%, Table 4.2), of whom 9 suffered from sacral anomalies, 1 from spinal anomalies and 2 from both (Table 4.3). Fourteen patients (33%) needed clean intermittent catheterization (CIC), of whom 7 had a Mitrofanoff diversion and 4 had spontaneous voiding, but needed intermittent catheterization to empty the bladder from residue. Of the 14 patients that needed CIC, 8 had associated sacral or spinal

Table 4.1 *Patient characteristics (n=42)*

Length common channel[a]	
Short (<3cm)	19 (76%)
Long (≥3cm)	6 (24%)
Associated anomalies	
Sacral anomalies	22 (52%)
Spinal anomalies	7 (17%)
Cardiac anomalies	14 (33%)
Esophageal atresia	8 (19%)
Renal anomalies	21 (50%)
Limb anomalies	11 (26%)
Müllerian structures	
duplicature	27 (64%)
agenesis	4 (10%)
Surgical approach	
PSARVUP	24 (57%)
Short CC[a]	*7 (17%)*
Long CC[a]	*4 (10%)*
TUM	18 (43%)
Short CC[a]	*12 (29%)*
Long CC[a]	*2 (5%)*

[a] Length of common channel was missing in 17 patients. Therefore, calculations were made for the 25 patients in whom common channel length was measured. PSARVUP posterior sagittal anorecto vagino urethroplasty; TUM total urogenital mobilization; CC common channel.

Table 4.2 *Urological and gynecological outcome in patients with cloacal malformations (n=42).*

	Short CC (n=19)	Long CC (n=6)	Total (n=42)[a]
Spontaneous voiding	16 (84%)	2 (33%)	29 (69%)
CIC	4 (21%)	3 (50%)	14 (33%)[b]
Urinary diversion	3 (16%)	2 (33%)	10 (24%)
Urethral continence	13 (68%)	5 (83%)	32 (76%)
Recurrent UTI	7 (37%)	5 (83%)	23 (55%)
Kidney transplantation	1 (5%)	1 (17%)	3 (7%)
Secondary vaginoplasty	3 (16%)	3 (50%)	9 (21%)
Normal menstruations[c]	4 (50%)	2 (100%)	11 (55%)

[a] Length of common channel was missing in 17 patients; [b]Four patients voided spontaneously, but needed intermittent catheterization to empty the bladder from residue; [c] Menstrual status was assessable in a total of 20 patients due to age, 8 of them had a short common channel, 2 a long common channel.
CC common channel; CIC clean intermittent catheterization; UTI urinary tract infections.

Table 4.3 *Urological outcome in patients with associated sacral or spinal anomalies.*

Associated anomalies		SV	CIC	UD
Sacral	Spinal			
no	no	17	6	2
yes	no	9	6	4
no	yes	1	0	0
yes	yes	2	2	4

SV spontaneous voiding; CIC clean intermittent catheterization; UD urinary diversion.

Table 4.4 *Urological and gynecological outcome in patients with short common channels; PSARVUP vs. TUM.*

	PSARVUP (n=7)	TUM (n=12)	p-value
Spontaneous voiding	5 (71%)	11 (92%)	0.523
Intermittent catheterization	2 (29%)	2 (17%)	0.603
Urinary diversion	2 (29%)	1 (8%)	0.523
Urethral continence	5 (71%)	8 (67%)	1.000
Recurrent UTI	3 (43%)	4 (33%)	1.000
Kidney transplantation	0 (0%)	1 (8%)	1.000
Secondary vaginoplasty	2 (29%)	1 (8%)	0.523
Normal menstruations [a]	1 (33%)	3 (60%)	1.000

[a] *Menstrual status was only assessable in 8 patients (3 PSARVUP, 5 TUM) due to age.*
PSARVUP posterior sagittal anorecto vagino urethroplasty; TUM total urogenital mobilization; UTI urinary tract infections.

anomalies. Urinary diversions were created in 10 patients (24%), 8 of them had associated sacrospinal anomalies.

In total 32 patients (76%) had no involuntary loss of urine per urethra. Recurrent urinary tract infections were seen in 23 patients (55%). Kidney transplantation due to end-stage renal failure was needed in 3 patients (7%), all of whom suffered from severe congenital renal anomalies. At latest follow-up no patients were on dialysis. When comparing types of surgical approach (PSARVUP vs. TUM) in patients with short common channels, there was no significant difference in urological outcome within the current period of follow-up (Table 4.4).

A secondary vaginoplasty due to severe vaginal stenosis was needed in 9 patients (21%, Table 4.2). Normal menstruations were present in 11 (55%) of the 20 patients who reached puberty. Primary amenorrhea was present in 2 patients (10%). In the patients without normal menstruations, oligomenorrhea was present in 2 (10%), hypermenorrhea in 2 (10%), and dysmenorrhea in 1 (5%). Three patients (15%) underwent surgery for hematometra as a consequence of an obstructed menstrual flow; 2 of them underwent total hysterectomy, the other patient underwent a hemi hysterectomy and had oligo-

menorrhea ever since. No pregnancies occurred in this series until now. As for urological outcome there were no differences in gynecological outcome when comparing surgical approaches in patients with short common channels (Table 4.4).

Discussion

Surgical repair of cloacal malformations is a challenge. After the introduction of the posterior sagittal approach in 1982 results for the repair of anorectal malformations improved.[2,10,11] Modification of the PSARVUP with the introduction of the total urogenital mobilization (TUM) for cloacal repair resulted in decreased operation time and a reduction of early postoperative complications.[4] It furthermore improved cosmetic results. TUM is presented as the first choice of reconstruction in cloacal malformations with an adequate length of both common channel (generally less than 3 cm) and urethra, which allow mobilization of the urogenital sinus to the perineum. In long common channels (>3 cm) often the PSARVUP is preferred, although sometimes a TUM is performed. We found more patients with long common channels in the PSARVUP group. This makes the comparison of outcome of both techniques prone to a bias in favor of the TUM-technique as these patients were more likely to be less complicated cases. We therefore compared both surgical techniques in patients with short common channels only and found no differences in urological and gynecological outcome between the two groups. Thus, performing a TUM does not seem to worsen urogenital outcome in patients with cloacal malformations, as was suggested previously.[6-8]

One of the major differences between PSARVUP and TUM lies in the dissection of the suspensory ligaments of the bladder neck and anterior urethra. It is thought that extensive dissection of the bladder neck during TUM may lead to dysfunctional voiding or urinary incontinence.[6-8] The extensive dissection can lower the bladder neck below the pelvic floor and then lead to difficulties in achieving urinary continence. Considering the retrospective nature of this study, the level of dissection was not always retrievable from the records. Generally, the level of dissection during surgery depends on the possibility of mobilizing the urethra and vagina tension free to the perineum. Many times a total mobilization was not necessary and the suspensory ligaments were not completely taken down. Although often referred to as TUM, it may be true that the surgical procedure was not a "total" but only a *"partial urogenital mobilization"* in some of the cases reviewed in our study. This would then have less impact on bladder function and then partly explain the better outcome of continence in TUM patients in our study. In a recent study comparing total and partial urogenital mobilizations, no differences in urological outcome were seen between both types of mobilization; according to their

results it might be concluded that the type of mobilization, total or partial, would not have affected the outcome in our series.[12]

No other studies have presented urogenital outcome comparing PSARVUP with TUM and as both techniques are now often used in different patient groups (PSARVUP for long common channels, TUM for short common channels), it is not likely that this matter will be studied in the future. Although our study is the first addressing this comparison, it does have certain limitations. First of all, it is a retrospective study and thus not all the needed data was retrievable (level of dissection, length of common channel). Further, it was a multi-center study, therefore chances on selection bias as well as surgeon variability are high. On the other hand, this is the first study ever to report on a nationwide survey of patients with cloacal malformations. Other studies regarding clinical outcome after TUM report urinary incontinence in 24-33% and intermittent catheterization in 50-100% of the patients.[6,13,14] Our study shows that spontaneous voiding is frequently seen both after TUM (92%) and after PSARVUP (71%) in patients with short common channels. No significant differences in need for intermittent catheterization and urinary diversion were seen between both groups, suggesting that TUM has no long-term disadvantage on bladder function and incontinence within the current period of follow-up. In total 33% of the patients in our series needed intermittent catheterization and 24% needed a urinary diversion. Two other large studies report comparable results: 24-28% of their patients need catheterization and 22% had an urinary diversion.[1,15]

Over half of the patients in our series suffered from recurrent urinary tract infections (UTI) with no significant difference between PSARVUP and TUM groups. Frequent UTI may lead to renal failure when treated inadequately or not treated at all.[16] Kidney transplantations due to end-stage renal failure were conducted in 3 of our patients (7%) within the current time frame, which is similar to 6% in another study.[16] Having recurrent UTI, as well as the high incidence of congenital renal anomalies (50%), makes these patients prone to deterioration of renal function. Adequate treatment of these infections thus is crucial. Currently, no standard monitoring of these patients for the presence of UTI is conducted. In children with neurogenic bladder a monitoring program for the presence of UTI has proven valuable.[17] Effectiveness of such a monitoring program in patients with cloaca should be subject of investigation in future studies.

Forty-seven percent of our patients had Müllerian structure anomalies, which can lead to obstruction of the menstrual blood flow at time of the menarche.[18] An obstructed menstrual flow leading to a hematometra was present in 15% of the post-puberty patients, all of whom needed a surgical intervention after menarche. Although 52% of our patients still have to reach puberty, 45% of those who did show physical signs of

puberty had abnormal or absent menstruations. Other studies reported similar results concerning gynecological function with only 32% of the patients having normal menstruations.[18,19] No differences were seen between PSARVUP and TUM patients. Genital anatomy is likely to be of greater importance in gynecological outcome for patients with cloacal malformations. Referral to a specialized (pediatric) gynecologist therefore is mandatory in all patients with cloacal malformations 6 months after first signs of puberty (thelarche).[20] Furthermore, items such as sexual and obstetric abilities as well as quality of life may be important factors of gynecological functioning. Our center is currently conducting a study that also accounts for these items and future studies in these patients should do likewise to be able to make a full assessment of gynecological functioning.

Conclusion

Urogenital functional outcome after reconstructive surgery for cloacal malformations was similar in PSARVUP and TUM groups in our patients with short common channels. More than half of the patients with cloacal malformations suffered from recurrent urinary tract infections. A thorough urological follow-up is needed to establish the long-term bladder function and urinary incontinence results. Albeit without differences between PSARVUP and TUM groups, 45% of the patients present with abnormal or absent menstruations. Gynecological follow-up is mandatory in all patients with cloacal malformations 6 months after the first sign of puberty.

References

1 Hendren WH. Cloaca, the most severe degree of imperforate anus: experience with 195 cases. Ann Surg 1998; 228: 331-346.

2 Pena A, Devries PA. Posterior sagittal anorectoplasty: important technical considerations and new applications. J Pediatr Surg 1982; 17: 796-811.

3 Pena A. The surgical management of persistent cloaca: results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg 1989; 24: 590-598.

4 Pena A. Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997; 32: 263-267.

5 Levitt MA, Pena A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg 2010; 19: 128-138.

6 Matsui F, Shimada K, Matsumoto F et al. Bladder function after total urogenital mobilization for persistent cloaca. J Urol 2009; 182: 2455-2459.

7 Ludwikowski B, Oesch Hayward I, Gonzalez R. Total urogenital sinus mobilization: expanded applications. BJU Int 1999; 83: 820-2.

8 Rink RC, Metcalfe PD, Cain MP et al. Use of the Mobilized Sinus with Total Urogenital Mobilization. J Urol 2006; 176: 2205-2211.

9 Versteegh HP, Sloots CEJ, de Jong JR et al. Early versus late reconstruction of cloacal malformations; the effects on postoperative complications and long-term colorectal outcome. J Pediatr Surg 2014; 49: 556-559.

10 Holschneider AM, Jesch NK, Stragholz E et al. Surgical methods for anorectal malformations from Rehbein to Pena--critical assessment of score systems and proposal for a new classification. Eur J Pediatr Surg 2002; 12: 73-82.

11 deVries PA, Pena A. Posterior sagittal anorectoplasty. J Pediatr Surg 1982; 17: 638-643.

12 Palmer BW, Trojan B, Griffin K et al. Total and partial urogenital mobilization: focus on urinary continence. J Urol 2012; 187: 1422-1426.

13 Braga LH, Lorenzo AJ, Dave S et al. Long-term renal function and continence status in patients with cloacal malformation. Can Urol Assoc J 2007; 1: 371-376.

14 Camanni D, Zaccara A, Capitanucci ML et al. Bladder after total urogenital mobilization for congenital adrenal hyperplasia and cloaca--does it behave the same? J Urol 2009; 182: 1892-1897.

15 Pena A, Levitt MA, Hong A et al. Surgical management of cloacal malformations: a review of 339 patients. J Pediatr Surg 2004; 39: 470-479.

16 Warne SA, Wilcox DT, Ledermann SE et al. Renal outcome in patients with cloaca. J Urol 2002; 167: 2548-2551.

17 Liptak GS, Campbell J, Stewart R et al. Screening for urinary tract infection in children with neurogenic bladders. Am J Phys Med Rehabil 1993; 72: 122-126.

18 Levitt MA, Stein DM, Pena A. Gynecologic concerns in the treatment of teenagers with cloaca. J Pediatr Surg 1998; 33: 188-193.

19 Warne SA, Wilcox DT, Creighton S et al. Long-term gynecological outcome of patients with persistent cloaca. J Urol 2003; 170: 1493-1496.

20 Breech L. Gynecologic concerns in patients with anorectal malformations. Semin Pediatr Surg 2010; 19: 139-145.

Chapter 5

Effects of reconstructive surgery on bladder function in patients with anorectal malformations.

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Abstract

Purpose Bladder dysfunction is common in patients with anorectal malformations, and can be congenital or acquired as a consequence of surgery. Aim of this study was to investigate effects of the surgical correction of anorectal malformations on bladder function.

Materials and methods Charts of all 341 patients who were operated in our center between 1990 and 2010 were retrospectively analysed for a video urodynamic study (VUDS) done in both the preoperative and postoperative period. Fifty-two patients were eligible. Each study was scored according to *International Children's Continence Society* standards.

Results In 36 patients (69%) the preoperative urodynamic study indicated normal bladder function, 37 patients (71%) had a normal VUDS after surgery. Median bladder emptying efficiency and relative bladder capacity changed significantly after the posterior surgery. Bladder function according to ICCS standards did not change after surgery in 43 patients (83%). In 1 of the 4 patients with a deterioration of bladder function, the deterioration can solely be attributed to the surgery. Clinical outcome was available in 38 patients and showed complete urinary continence with spontaneous voiding in 24 patients (63%). Seven of 25 patients (28%) with a preoperative VUDS indicating normal bladder function showed dysfunctional voiding at latest follow-up.

Conclusions Urodynamic and clinical outcome in patients after anorectal malformation repair is good with 63% of the patients being continent for urine. Urodynamic studies are of limited value in preoperative settings in these patients. Current techniques for reconstructive surgery in anorectal malformations seem to preserve bladder function in the majority of patients.

Introduction

Congenital anorectal malformations (ARM) comprise a spectrum of malformations ranging from mild to very complex anatomical abnormalities.[1] In mild malformations a fistula is found between the rectum and the perineum (rectoperineal fistula). The spectrum continues from a rectourethral fistula to a bladder neck fistula in males, and from a vestibular fistula to a cloacal malformation in females. Both mild and complex malformations are usually repaired in the first years of life. Currently, the most widely used technique to repair ARM is the posterior sagittal anorectoplasty (PSARP) introduced by Peña in the early eighties of the last century.[2] In some cases, e.g. bladderneck fistulas, the PSARP is combined with a laparotomy or laparoscopy for more extensive dissection. For the repair of a cloacal malformation the PSARP is extended with either a vagino urethroplasty (PSARVUP), to divide the urogenital sinus, or a total urogenital mobilization (TUM), to mobilize the urogenital sinus *en bloc* to reach the perineum.[3,4] The aim of the surgical correction is to achieve optimal anorectal, urological, and gynecological function. In ARM, however, bladder dysfunction is often encountered both preoperatively and postoperatively. Long-term follow-up shows that up to 24-52% of the ARM patients suffer from severe bladder dysfunction, which might result in urinary incontinence, recurrent urinary tract infections, or, in some cases, even end-stage renal failure.[5-7] It is controversial whether bladder dysfunction is congenital or the result of surgery in patients with ARM.[8,9] Purpose of this study is to investigate whether the anorectal reconstruction itself influences bladder function in patients with ARM.

Patients and methods

The database of our pediatric urology department was retrospectively queried for patients with ARM who were operated on between 1990 and 2010. Fifty-two of 341 patients underwent a video urodynamic study (VUDS) both before as well as after reconstructive surgery. In general, these were patients with more complex malformations, in whom urodynamic studies were conducted according to protocol. In most patients with mild malformations preoperative and postoperative VUDS were not conducted, unless urological status indicated the need for urodynamics.

Patient records were screened for congenital lumbosacral bone deformities, spinal cord anomalies diagnosed by ultrasound or MRI, mental disabilities, and urological anomalies. VUDS were carried out according to standardised protocol following the international guidelines regarding urodynamic studies.[10] Bladder emptying efficiency was calculated as the voided volume divided by the voided volume plus the residual volume.

Relative bladder capacity was calculated as the measured bladder capacity divided by the expected bladder capacity. Expected bladder capacity was calculated according to the formula: 30+(30 × age in years) = capacity in ml.[11]

Bladder function according to the VUDS was scored by a pediatric urologist (KW) using a classification derived from *International Children's Continence Society* standards.[12] Bladder function was classified in 4 levels, being: 1. normal bladder function, 2. detrusor underactivity, 3. detrusor overactivity, 4 detrusor sphincter dyssynergia. Clinical urological outcome during the most recent follow-up was documented. For analyses we compared preoperative and postoperative data. Statistical analyses were done using SPSS 17; medians were compared using a Wilcoxon signed ranks test.

Results

Patient characteristics

ARM were diagnosed as perineal fistulas (n=3), bulbar rectourethral fistulas (n=4), prostatic rectourethral fistulas (n=20), and bladder neck fistulas (n=3) in male infants and as vestibular fistulas (n=12), and cloacal malformations (n=10) in female patients. Sacral bone deformities were seen in 23 patients (44%). Spinal cord anomalies were seen in 6 patients (12%); 5 patients (10%) had combined sacral and spinal anomalies. Abnormalities in renal anatomy were found in 12 patients (24%) and hypospadias in 6 males. Trisomy 21 was seen in 3 patients (6%); 3 other patients had an unspecified mental retardation without chromosomal anomalies. Surgical reconstruction was performed at a median age of 10 months (range 2-31 months). In all patients a posterior sagittal approach was used for reconstructive surgery.[2,3] Four of 10 patients with a cloacal malformation underwent a PSARVUP; in the other 6 a TUM was done. In 9 of 52 patients (17%) the posterior approach was combined with a laparotomy and in 6 (12%) with a laparoscopy for extensive rectal mobilisation.

Video Urodynamics

Preoperative VUDS were conducted at a median age of 5 months (range 0-19). Median time between surgery and postoperative VUDS was 7 months (range 0-83). Median bladder emptying efficiency decreased from 88% (range 0-100%) preoperatively to 53% (range 0-100%) after surgery (p=0.021). Relative bladder capacity increased from 121% (range 18-273%) to 139% (range 19-390%) after the posterior approach (p=0.017). Vesico ureteral reflux was seen in 22 patients (42%) before surgery, in 20 (39%) after surgery. Of the 22 patients who had preoperative reflux, 13 had persistent reflux after surgery. Furthermore, 7 patients with no reflux before surgery were found to have reflux during

Table 5.1 *Outcome of preoperative and postoperative VUDS according to ICCS standards.*

	Normal		UD		OD		DSD	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
No sacral or spinal anomalies (n=28)	21	22	0	1	6	4	1	1
Sacral and/or spinal anomalies (n=24)	15	15	0	1	9	7	0	1
Total (n=52)	36	37	0	2	15	11	1	2

Preop preoperative; Postop postoperative; UD underactive detrusor; OD overactive detrusor; DSD detrusor sphincter dyssynergia.

the postoperative VUDS. Before surgery bladder function according to ICCS standards was interpreted as normal in 36 patients (69%), overactive detrusor function was seen in 15 (29%), and DSD in 1 patient (2%, Table 5.1). After the posterior sagittal reconstruction bladder function was interpreted as normal in 37 (71%), underactive detrusor function in 2 (4%), overactive detrusor function in 11 (21%), DSD in 2 (4%, Table 5.1). In 9 patients (17%) bladder function according to urodynamic outcome had changed after surgery; bladder function improved in 5, however, it worsened in 4. In the 4 patients with deteriorated function, 1 had a cloacal malformation that was corrected using a urogenital mobilization, 2 were male patients with bulbar fistulas, and 1 male had a prostatic fistula who was operated on with a laparotomy assisted procedure. One out of 4 patients who showed a deterioration of bladder function had sacral vertebral anomalies.

Clinical outcome

Clinical outcome was available in 38 patients with a median period of follow-up of 109 months (range 30-240). Seven patients were lost in follow-up and another 7 patients were not yet potty trained. Complete urinary continence with spontaneous voiding was achieved in 24 patients (63%, Table 5.2), of whom 15 had no lumbosacral or spinal anomalies. Eight patients (21%) needed clean intermittent catheterization (CIC), of

Table 5.2 *Clinical outcome per type of malformation (n=38).*

	Continent	CIC	Incontinent
Perineal fistula (n=2)	1	1	0
Bulbar fistula (n=3)	1	1	1
Prostatic fistula (n=11)	9	1	1
Bladder neck fistula (n=2)	1	1	0
Vestibular fistula (n=11)	8	0	3
Cloacal malformation (n=9)	4	4	1
Total	24	8	6

CIC Clean intermittent catheterization

whom 2 used a continent Mitrofanoff channel. Five patients on CIC had no sacral or spinal anomalies. Of the patients on CIC 2 suffer occasional loss of urine per urethra. Regardless of the use of CIC, all patients with overactive detrusor function also received anticholinergic treatment. Complete urinary incontinence was seen in 6 patients (16%); 2 without sacral or spinal anomalies, 4 with either sacral anomalies, spinal anomalies, or both. Recurrent urinary tract infections were reported in 10 patients (19%), 5 patients (10%) underwent endoscopic treatment for vesico ureteral reflux. Two patients (4%) with a small capacity and poor compliant bladder were finally treated with a bladder augmentation after initial treatment with a vesicostomy with ongoing complications (such as reflux or recurrent UTI). One patient (2%) with a cloacal malformation developed end-stage renal failure and received a kidney transplant.

When comparing VUDS outcome with functional clinical outcome for the 38 patients in whom this was available, the majority of patients with normal VUDS achieved continence (18 of 25 preoperative VUDS, 21 of 25 postoperative VUDS, Table 5.3). Seven of 25 patients (28%) with a preoperative VUDS indicating normal bladder function showed dysfunctional voiding at latest follow-up. Six of 13 patients with an abnormal VUDS before surgery were continent with no dysfunctional voiding at follow-up, the other 7 either were on CIC or were suffering from incontinence.

Table 5.3 *VUDS outcome compared to functional clinical outcome (n=38).*

	Preoperative				Postoperative			
	Normal	UD	OD	DSD	Normal	UD	OD	DSD
Continent	18	0	6	0	21	0	2	1
CIC	3	0	4	1	1	2	4	1
Incontinent	4	0	2	0	3	0	3	0

UD underactive detrusor; OD overactive detrusor; DSD detrusor sphincter dyssynergia.

Of the 4 patients with deterioration of bladder function after surgery, 3 also had impaired urological function at follow-up: 2 empty their bladder with CIC and 1 is continuously incontinent for urine. However, among the patients with a deterioration of bladder function, 1 has Down's syndrome and 1 is known with a non-chromosomal mental retardation. The fourth patient with worsened bladder function had sacral anomalies. An intensive program of pelvic floor physiotherapy resulted in complete continence in this patient.

In the TUM group for cloacal repair 1 patient improved from an idiopathic overactive bladder to a normal bladder, while 1 other patient deteriorated from a normal bladder to a full neurogenic bladder with detrusor underactivity and is now in need of CIC. None

of the 4 patients who were operated on with PSARVUP had a bladder function impairment after surgery.

Discussion

Patients with ARM suffer from urogenital tract dysfunction in up to 52% of the cases.[7] The most important causes of this dysfunction are congenital anomalies of the urogenital tract, neurological disturbances due to sacral agenesis, partial sacral vertebral anomalies and spinal dysraphism (e.g. tethered cord). However, it is controversial whether bladder dysfunction is congenital only or also the result of surgery.[8] VUDS are generally performed in order to evaluate storage and emptying capability of the bladder and to investigate causes of urinary incontinence and urinary tract infections. In this study the effects of the posterior sagittal approach on bladder function was studied using preoperative and postoperative VUDS related to clinical urological outcome. VUDS, however, are often subject to artefacts that may influence interpretation and should therefore be assessed by experienced pediatric urologists in order to be a useful tool for diagnostic assessment and follow-up.[13] Another limitation of the study is its retrospective design, which is known to influence the outcome of the study. Furthermore, sample size of the study is rather small. A larger, prospective study is needed to verify the results as stated in our study. On the other hand, our study is one of the first ever to give insight in the discussion regarding worsening bladder function after surgery for ARM.

After surgical repair of the anorectal malformation bladder function remained unchanged in the majority of our patients (83%). Nine patients encountered a change in bladder function: 5 an improvement and 4 an impairment. In another study deterioration of bladder function was only observed in patients with a cloacal malformation.[9] The authors suggest, as was proposed in an earlier study, that in the long common channel cloacas a higher mobilization of the bladder neck and upper vagina gives minor damage to pre-existing clinically irrelevant nerve abnormalities resulting in these clinical effects.[8] The latter is also suggested to occur using a TUM in cloaca repair, in which mobilization of the bladder neck below the pelvic floor during the TUM may lead to more urinary incontinence than after a PSARVUP.[9,14] In our study, in the PSARVUP group none of the patients had a deterioration of bladder function. In the TUM group (n=6), 1 patient improved and 1 patient deteriorated from a normal bladder function before surgery to a neurogenic bladder (underactive detrusor) after surgery. The other 4 remained unchanged after surgery suggesting no negative effects of surgery. In another study urodynamics conducted after cloacal repair showed bladder dysfunction in all patients after conducting reconstructive surgery.[14] However, this study did not compare

urodynamic results both before and after surgery. Results of studies comparing TUM for cloacal repair with TUM for congenital adrenal hyperplasia and isolated UGS also showed that the TUM itself did not trigger impairment of urodynamic and functional outcome.[15,16] TUM includes ligation of the suspensory ligaments of the bladder.[3] Thus lowering of the bladder neck, possibly below the pelvic floor, is the major drawback of this technique for urological outcome. In most of our cases (personal notes) it was unnecessary to completely ligate the suspensory ligaments for urogenital mobilisation and this might flatter the urological outcome. Our series are too small to give absolute evidence that there are no major changes in bladder function after surgery, either PSARVUP or TUM, but we consider both PSARVUP and TUM to be good techniques for the repair of cloacal malformations. In general, reconstructive surgery for ARM does not seem to deteriorate bladder function in our series.

When it is taken into account that this study included patients with the more complex ARM, clinical outcome was generally good with 63% of the patients being continent for urine. Although surgery did not alter bladder function in most of our patients, VUDS data showed that bladder emptying efficiency decreased and relative bladder capacity increased significantly after conducting reconstructive surgery. The authors have no clear explanation for these findings, other than that increased bladder capacity may have resulted in a decrease in efficiency. Another study found similar changes in emptying efficiency and relative capacity after posterior sagittal surgery.[9] Significant changes in VUDS measurements thus do not necessarily correlate to changes in bladder function according to ICCS standards. Further, bladder function according to ICCS standards does not always correlate with clinical urological outcome. These matters raise questions regarding clinical value of VUDS in patients with ARM, particularly in the preoperative setting. VUDS has been proven of limited use in selected populations with poor prognostic value in preoperative settings.[17] The same may be true in our population, with 7 patients (50%) of 14 who showed impaired clinical urological outcome despite initial normal bladder function during preoperative VUDS. Six of 13 patients with an abnormal VUDS before surgery were continent with no dysfunctional voiding at follow-up. Of the 14 patients with dysfunctional voiding at follow-up 4 (29%) had a postoperative VUDS indicating normal bladder function. Especially preoperative VUDS seems to be of limited value in these patients. The use of other radiological diagnostics, e.g. ultrasound for the diagnosis of ureteral dilation and bladder wall thickness are sufficient in these patients before surgery to bridge the time to final reconstruction. In case of continuing urological dysfunction after surgical reconstruction VUDS might be a useful diagnostic tool.

Conclusion

In 83% of the patients with an anorectal malformation bladder function remained unchanged after reconstructive surgery. Urodynamic and clinical outcome in patients after anorectal malformation repair is generally good with 63% of the patients being continent for urine. Urodynamic studies are of limited value in preoperative settings in these patients but are useful in the follow-up of on-going urological dysfunction after surgery in patients with anorectal malformations.

References

1. Levitt MA, Pena A. Anorectal malformations. Orphanet J Rare Dis 2007; 2: 33.
2. Pena A, Devries PA. Posterior sagittal anorectoplasty: important technical considerations and new applications. J Pediatr Surg 1982; 17: 796-811.
3. Pena A. Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997; 32: 263-267.
4. Pena A. The surgical management of persistent cloaca: results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg 1989; 24: 590-598.
5. Levitt MA, Pena A. Outcomes from the correction of anorectal malformations. Curr Opin Pediatr 2005; 17: 394-401.
6. Senel E, Akbiyik F, Atayurt H et al. Urological problems or fecal continence during long-term follow-up of patients with anorectal malformation. Pediatr Surg Int 2010; 26: 683-689.
7. Goossens WJ, de Blaauw I, Wijnen MH et al. Urological anomalies in anorectal malformations in The Netherlands: effects of screening all patients on long-term outcome. Pediatr Surg Int 2011; 27: 1091-1097.
8. Boemers TM, Bax KM, Rövekamp MH et al. The effect of posterior sagittal anorectoplasty and its variants on lower urinary tract function in children with anorectal malformations. J Urol 1995; 153: 191-193.
9. Warne SA, Godley ML, Wilcox DT. Surgical reconstruction of cloacal malformation can alter bladder function: a comparative study with anorectal anomalies. J Urol 2004; 172: 2377-2381.
10. Schäfer W, Abrams P, Liao L et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn 2002; 21: 261-274.
11. Holmdahl G, Hanson E, Hanson M et al. Four-hour voiding observation in healthy infants. J Urol 1996; 156: 1809-1812.
12. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003; 61: 37-49.
13. Nijman RJ. Pitfalls in urodynamic investigations in children. Acta Urol Belg 1995; 63: 99-103.
14. Matsui F, Shimada K, Matsumoto F et al. Bladder function after total urogenital mobilization for persistent cloaca. J Urol 2009; 182: 2455-2459.
15. Camanni D, Zaccara A, Capitanucci ML et al. Bladder after total urogenital mobilization for congenital adrenal hyperplasia and cloaca--does it behave the same? J Urol 2009; 182: 1892-1897.
16. Palmer BW, Trojan B, Griffin K et al. Total and partial urogenital mobilization: focus on urinary continence. J Urol 2012; 187: 1422-1426.
17. Theofrastous JP, Whiteside J, Paraiso MF. The utility of urodynamic testing. J Am Assoc Gynecol Laparosc 2003; 10: 548-552.

Chapter 6

Postoperative complications after reconstructive surgery for cloacal malformations: a systematic review.

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Abstract

Purpose The repair of cloacal malformations is most often performed using a posterior sagittal anorecto-vagino-urethroplasty (PSARVUP) or total urogenital mobilization (TUM) with or without laparotomy. Aim of this study was to systematically review the frequency and type of postoperative complications seen after cloacal repair as reported in literature.

Methods A systematic literature search was conducted according to PRISMA guidelines for preferred reporting of systematic reviews and meta-analyses. Eight records were eligible for this study which were qualitatively analysed according to the Rangel score.

Results Overall complication rates reported in included studies ranged from 0% to 57%. After meta-analysis of data, postoperative complications were seen in 99 of 327 patients (30%). Most common reported complications were recurrent or persistent fistula (n=29, 10%) and rectal prolapse (n=27, 10%). In the PSARVUP group complication rate was 40%, in the TUM group 30% ($p = 0.205$).

Conclusion This systematic review shows that postoperative complications after cloacal repair are seen in 30% of the patients. The complication rates after PSARVUP and TUM were not significantly different. Standardisation in reporting of surgical complications would inform further development of surgical approaches. Other techniques aiming to lower postoperative complication rates may also need consideration.

Background

Patients with a congenital cloacal malformation undergo complex reconstruction of the recto-urogenital tracts. The current surgical approach for cloacal repair was derived from the posterior sagittal anorectoplasty (PSARP), described by Peña and De Vries in 1982.[1,2] This posterior sagittal anorecto-vagino-urethroplasty (PSARVUP) extended the anorectoplasty with a meticulous dissection of the combined vaginal-urethral walls, followed by a reconstruction of distal parts of both structures.[3] In 1997 the total urogenital mobilization (TUM) was presented by Peña, mooting a new, faster, surgical approach for certain cases of cloacal repair with better cosmetic results.[4] In TUM the urogenital sinus is not divided into vaginal and urethral components, but mobilized *en bloc* to reach the perineum. Before the introduction of these current techniques, treatment prioritised anorectal sphincter reconstruction, yet in this period fecal incontinence was the main long-term postoperative problem.[5] Using posterior sagittal approaches – with or without the TUM – long-term outcome of continence improved considerably, but constipation or obstructive defecation became an increasingly serious problem.[6] One factor that can negatively influence final functional outcome in patients with cloacal malformations is the need for reoperations due to postoperative complications.[7] Not only is the first chance most often the best chance to deliver a good outcome, but each trip to theatre carries a significant burden, both physical, psychological and potentially financial, on the patient and her carers. Postoperative complications following cloacal repair have received relatively little attention. Here, we systematically reviewed current literature reporting postoperative complications following cloacal repair. In this study we aimed to develop our understanding of postoperative complications in one of the most complex congenital malformations requiring surgical intervention.

Methods

For the systematic review of literature we followed the PRISMA statement, checklist and flow-chart were used in order to achieve the highest standard in reporting items for a systematic review and meta-analysis.[8,9]

Search strategy

A systematic literature search was conducted on April 19th 2014 using the PubMed, EMbase, and Web-of-Science databases. Studies were searched in PubMed using the following search terms: *(cloacal malformations OR persistent cloaca) AND complications NOT exstrophy.* For the other databases appropriate search terms were applied concerning the postoperative outcome of patients with cloacal malformations.

Eligibility criteria

All studies that reported postoperative complications of patients with a cloacal malformation were included. No limits were set with regard to date of publication. Case report studies were excluded. Further, studies on the subject of anorectal malformations in general were only included when presenting a defined group of patients with a cloacal malformation, with the results regarding postoperative complications reported separately from the other anorectal malformations. All references of the articles we found were reviewed to include any further useful studies. Different articles that presented identical or overlapping outcome of the same study population were excluded.

Study selection

The study selection consisted of four separate processes: 1. Study identification, 2. Study screening, 3. Study eligibility, 4. Study inclusion. All processes were conducted by two separate reviewers (HV, IdB). Disagreements between reviewers were resolved by consensus.

Quality assessment

Quality of the articles was scored using the checklist as proposed by Rangel *et al*.[10] The checklist consisted of 3 subscales containing 30 items in total. The 3 subscales were: 1. Potential Clinical Relevance, 2. Quality of Study Methodology, and 3. Quality of Discussion and Stated Conclusions. A maximum of 45 points could be scored. Scores ranging from 0-15 indicated a study of poor quality, studies scoring from 16-30 points were considered to be fair and scores of 31 points or higher indicated a good study.

Data extraction

Two reviewers (HV,IdB) used predefined criteria to extract the data from included publications. The predefined criteria concerned study design, population, surgical data, and details on postoperative complications.

Statistical analysis

Data were analysed using SPSS (version 17; SPSS, Chicago, IL). Groups were compared using a Fisher's exact test.

Results

Study selection

Adequate search terms were used for each database and resulted in 107 records (PubMed), 142 records (EMbase), and 69 records (Web of Science). After the removal

of duplicates 227 records were identified from the 3 databases. A total of 177 records were deemed irrelevant based on the title, and excluded. Subsequently, 42 records were excluded for not meeting the inclusion criteria after assessing the abstract (n=29) or the full text (n=13, Fig. 6.1). Finally, 8 studies met inclusion criteria and were used for qualitative synthesis.

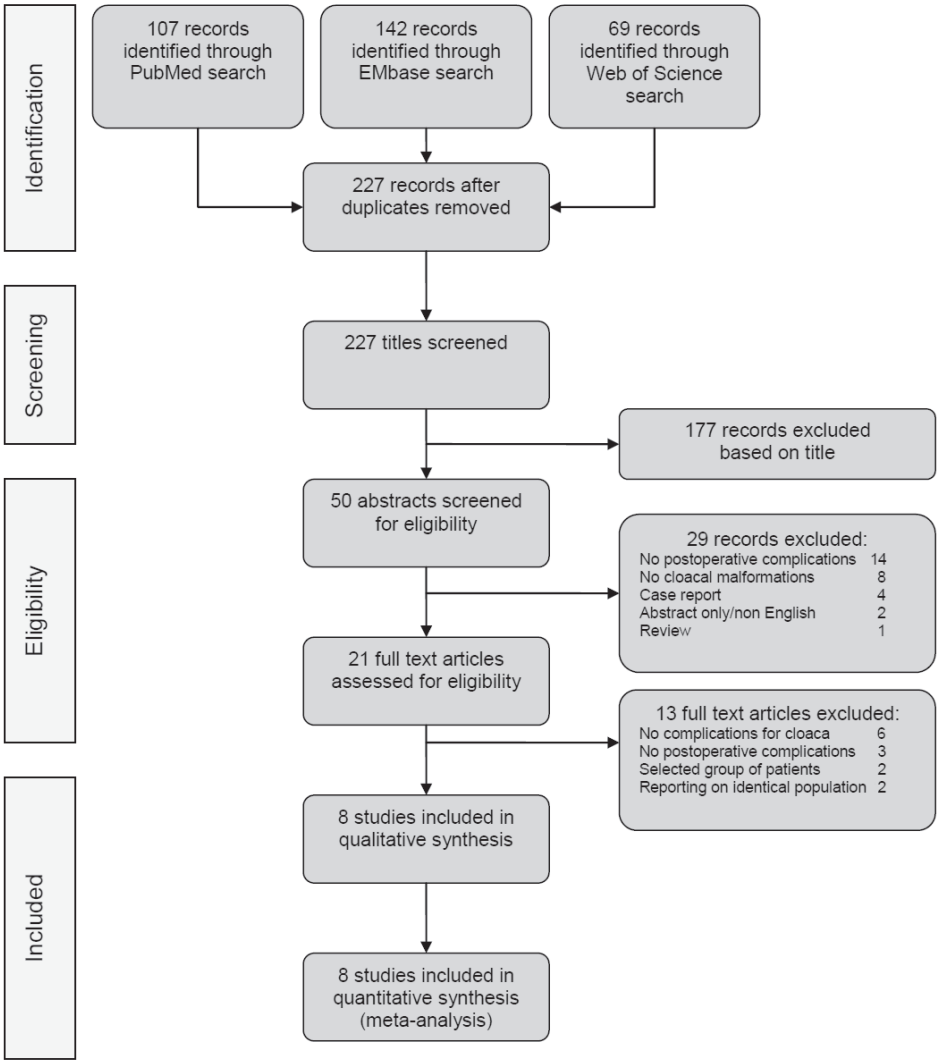

Figure 6.1 *Flowchart describing systematic literature search*

Study characteristics

Seven of eight studies comprised retrospective chart studies; one center conducted an observational cohort study[11] in which a laparoscopic rectal pull-through was conducted in 10 consecutive patients with cloacal malformations (Table 6.1). Study quality according to Rangel's score ranged from 10 to 31 points. A total of 597 patients were presented in the 8 studies with a median of 10.5 patients per study (range 6 – 490). However, in the largest study postoperative complications were only reported in the 220 TUM patients. One study reported that they assessed the postoperative complications within a period of 30 days after surgery, the other studies did not report a range of time in which the complications were assessed.[12]

Table 6.1 *Study characteristics.*

Author	*Country*	*Journal*	*Year*	*Sample size*	*Type of surgery*	*Quality*
Cho[14]	South Korea	J Korean Surg Soc	2011	9	PSARVUP[a]	12
Julià[18]	Spain	Pediatr Surg Int	2010	6	PSARP[b]	19
Leclair[16]	UK	J Urol	2007	22	TUM[c]	19
Levitt[13]	USA	Semin Pediatr Surg	2010	490[e]	PSARVUP/TUM	16
Liem[11]	Vietnam	J Pediatr Surg	2012	10	LRP[d]	16
Matsui[17]	Japan	J Urol	2009	11	TUM	20
Nakayama[15]	USA	J Pediatr Surg	1987	7	PSARVUP	10
Versteegh[12]	Netherlands	J Pediatr Surg	2014	42	PSARVUP/TUM	31

[a] posterior sagittal anorecto vagino urethroplasty; [b] posterior sagittal anorecto plasty; [c] total urogenital mobilization; [d] laparoscopic rectal pull-through; [e] complications were only reported in the 220 TUM patients.

Type of surgery and postoperative complications

In 2 studies both the PSARVUP and the TUM were used for cloacal reconstruction.[12,13] Two studies reported the use of PSARVUP only[14,15]; in 2 series only TUM was used.[16,17] In 1 study, patients were operated on by laparoscopic rectal pull-trough, without initial urogenital reconstruction.[11] Julià *et al.* described their series of patients with anorectal malformations, all of whom were reconstructed by posterior sagittal approach.[18] No details according to type of cloacal reconstruction used were reported.

The reported percentages of total postoperative complications ranged from 0 to 57% (Fig. 6.2). Pooled data showed that postoperative complications were seen in 99 of 327 patients (30%). In the PSARVUP group complication rate was 40%, in the TUM group 30% ($p = 0.205$, Table 6.2). Most common reported complications were recurrent or persistent fistula (n=29, 10%, Table 6.3), rectal prolapse (n=27, 10%), and vaginal complications (such as stenosis, stricture or occlusion, n=25, 9%). In the recurrent or persistent fistula group, 21 were urethrovaginal fistulas, 4 were persistent urogenital sinuses, 2 were rectovaginal fistulas, and a vesicovaginal fistula and a rectoperineal fistula were seen 1 time

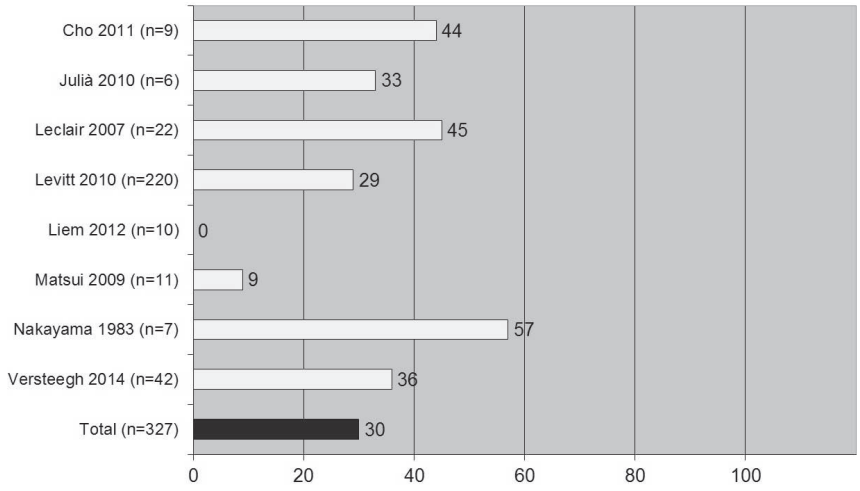

Figure 6.2 *Pooled data of complications (%) reported in included studies.*

Table 6.2 *Complications per type of cloacal repair*

	PSARVUP[a] (n= 40)		TUM[b] (n = 271)		p-value
	n	%	n	%	
Complications	16	40	81	30	0.205

[a] *Pooled data of Cho et al, Nakayama et al, Versteegh et al.*

[b] *Pooled data of Leclair et al, Levitt et al, Matsui et al, Versteegh et al.*

Table 6.3 *Complication rates per type of complication.*

Study	Patients with compl.[a]	Recurrent/ persistent fistula or UGS[b]	Rectal prolapse	Vaginal stricture/ stenosis	Wound dehiscence	Urethral stricture/ stenosis	Anal stricture/ stenosis
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cho (n=9) [14]	4 (44%)	2 (22%)				1 (11%)	
Julià (n=6) [18]	2 (33%)			2 (33%)			
Leclair (n=22) [16]	10 (45%)	4 (18%)		3 (14%)		2 (9%)	5 (23%)
Levitt (n=220) [13]	63 (29%)	13 (6%)	26 (12%)	18 (8%)		6 (3%)	
Liem (n=10) [11]	0 (-%)						
Matsui (n=11) [17]	1 (9%)			1 (9%)			
Nakayama (n=7) [15]	4 (57%)	3 (43%)		1 (14%)	1 (14%)		
Versteegh (n=42) [12]	15 (36%)	7 (17%)	1 (2%)		8 (19%)		
Total (n=327)	99 (30%)	29 (10%)	27 (10%)	25 (9%)	9 (18%)	9 (3%)	5 (23%)

[a] *Some patients suffered from more than 1 complication;* [b] *UGS urogenital sinus.*

each. In 4 of the studies, indications for reoperations were reported, with 11/17 (65%) patients experiencing complications requiring one or more additional procedures.[14,16-18] Nakayama et al reported that a secondary repair of their 3 patients with urethrovaginal fistula was being planned.[15] Levitt *et al.* reported the institutional experience from a major referral center. Secondary surgery was required in 93 patients who had undergone primary surgical repair elsewhere.[13] In this series, indications for reoperations were: rectal problems (such as prolapse, stricture, retraction, dehiscence or atresia) in 51 patients, persistent urogenital sinus in 39 patients, vaginal complications (stricture, retraction, dehiscence, atresia, or stenosis) in 34, a mislocated rectum in 29. Sixteen had urethrovaginal or rectovaginal fistulas, and 5 had urethral stricture or atresia. In addition to the recto-urethro-vaginal complications, Cho et al. also reported the occurrence of bladder or urethral stones in 2 of their patients.[14]

Discussion

The surgical reconstruction of anorectal malformations has changed over the years.[6] With the introduction of the posterior approach by Peña a thorough, reproducible work-up of patients with these anomalies was established.[1] In 1997 the introduction of the total urogenital mobilization (TUM) decreased operation time and resulted in better cosmetic results.[4] Although many studies that have evaluated cloacal reconstruction have mainly focused on long-term results, this review evaluates reported postoperative complications.

Postoperative complications often require surgical treatment for this group of patients but reoperative surgery may decrease functional outcome in patients with anorectal malformations.[7] Therefore, we assessed the number and origin of postoperative complications as a consequence of cloacal reconstruction in current literature.

Our systematic literature search interrogated 3 separate literature databases with 8 eligible studies subsequently found. In these studies complication rates ranged from 0-57% with a total complication rate of 30% in 327 patients with cloacal malformations. Recurrent or persistent fistula was the most frequently reported complication occurring in 29 (10%) of the patients in whom this was assessed.

One caveat is that complications may have been under reported; types of complications were not standardised, with each study reporting its own set of complications. Therefore, it is unclear if failure to report a complication equated to absence of the complication for any specific study.

Wound dehiscences, for example, were only reported in 2 studies (14-19%).[12,15] It seems unlikely that there were no wound dehiscences in any of the other studies. We would advocate that adequate reporting of postoperative complications in cloacal repair should at least comprise the number of recurrent or persistent fistulas or urogenital sinuses, rectal prolapses, wound dehiscences, and stricture or stenosis of reconstructed structures.

Not all studies reported whether complications were indications for reoperations. Since the need for reoperations is likely to influence outcome, these might be of more importance than the occurrence of the complications itself.[19] We encountered several other limitations while conducting this review; only one study reported the length of the postoperative period in which complications were assessed[12], and 7/8 studies were retrospective observations. The publication of the first study (1987) and the last study (2014) was such that surgical practice, as well as neonatal and pediatric postoperative care, and radiological evaluation will have changed in this time. We were only able to address the difference in surgical techniques, rather than non-surgical management that occurred in this period.

The 2 principle techniques did not demonstrate significant differences in complication rates (40% vs. 30%, p=0.205). It is likely that there will be other differences between centers, such as in clinical experience, that will affect outcome, making comparison difficult. Also, it should be taken into account that the TUM is generally used for less complex cases making complications less likely in this group. When comparing the largest cohort in this study[13] with all the other studies, a significant difference in complication rate was not seen (29% vs. 34%, p=0.371). However, this center serves as a major referral center, which suggests their population might be more complex compared to other centers.

Although TUM has been presented as an easier way to repair cloacal malformations with a shorter operation time, this approach can only be conducted in selected types of cloacal anatomy with a limited length of common channel. To our knowledge, both techniques for cloacal reconstruction have never been compared for the occurrence of postoperative complications. With this systematic review including our own 25-year experience we have demonstrated that complication rates after TUM are slightly lower than after PSARVUP, although the difference is not significant (p=0.205).

With respect to postoperative complications, both PSARVUP and TUM are adequate techniques to reconstruct recto-urogenital anatomy in patients with cloacal malformations, although a complication rate of 30% could be considered to be high. Recently, laparoscopic cloacal repair has been used to perform anorectal reconstruction.[11] In

the limited series presented (n=10) the authors did not encounter any postoperative complications, however, a second procedure was needed for urogenital reconstruction in these patients. Depending on the capabilities of the surgeon, laparoscopic cloacal repair should be investigated as future surgical approach of first choice. Furthermore, the field of tissue engineering, known for clinical solutions in degenerative diseases, has recently also made progress in the treatment of congenital conditions.[20,21] This novel field is developing rapidly and should be investigated in relation to improved treatment of complex congenital anomalies, such as cloacal malformations.

Conclusion

The complex surgical reconstruction of cloacal malformations has changed over the years and is generally done by PSARVUP or TUM. This systematic review shows that postoperative complications after cloacal repair are seen in 30% of the patients. There appeared to be no difference in complication rates between PSARVUP and TUM. The reporting of postoperative complications should be more uniform in order to find out their origin. Laparoscopic surgery and tissue engineering are matters that should be investigated as possible clinical developments for the future.

References

1. Pena A, Devries PA. Posterior sagittal anorectoplasty: important technical considerations and new applications. J Pediatr Surg 1982; 17: 796-811.
2. Devries PA, Pena A. Posterior sagittal anorectoplasty. J Pediatr Surg 1982; 17: 638-643.
3. Pena A. The surgical management of persistent cloaca: results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg 1989; 24: 590-598.
4. Pena A. Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997; 32: 263-267.
5. Stephens FD. Imperforate rectum; a new surgical technique. Med J Aust 1953; 1: 202-203.
6. Holschneider AM, Jesch NK, Stragholz E et al. Surgical methods for anorectal malformations from Rehbein to Pena--critical assessment of score systems and proposal for a new classification. Eur J Pediatr Surg 2002; 12: 73-82.
7. Levitt MA, Bischoff A, Pena A. Pitfalls and challenges of cloaca repair: how to reduce the need for reoperations. J Pediatr Surg 2011; 46: 1250-1255.
8. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
9. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
10. Rangel SJ, Kelsey J, Colby CE et al. Development of a quality assessment scale for retrospective clinical studies in pediatric surgery. J Pediatr Surg 2003; 38: 390-396.
11. Liem NT, Quynh TA. Laparoscopic rectal pull-through for persistent cloaca: an easier approach for a complex anomaly. J Pediatr Surg 2012; 47: 815-818.
12. Versteegh HP, Sloots CEJ, de Jong JR et al. Early versus late reconstruction of cloacal malformations: The effects on postoperative complications and long-term colorectal outcome. J Pediatr Surg 2014; 49: 556-559.
13. Levitt MA, Pena A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg 2010; 19: 128-138.
14. Cho MJ, Kim TH, Kim DY et al. Clinical experience with persistent cloaca. J Korean Surg Soc 2011; 80: 431-436.
15. Nakayama DK, Snyder HM, Schnaufer L et al. Posterior sagittal exposure for reconstructive surgery for cloacal anomalies. J Pediatr Surg 1987; 22: 588-592.
16. Leclair MD, Gundetti M, Kiely EM et al. The surgical outcome of total urogenital mobilization for cloacal repair. J Urol 2007; 177: 1492-1495.
17. Matsui F, Shimada K, Matsumoto F et al. Bladder function after total urogenital mobilization for persistent cloaca. J Urol 2009; 182: 2455-2459.
18. Julia V, Tarrado X, Prat J et al. Fifteen years of experience in the treatment of anorectal malformations. Pediatric Surgery International 2010; 26: 145-149.
19. Pena A, Grasshoff S, Levitt MA. Reoperations in anorectal malformations. J Pediatr Surg 2007; 42: 318-325.

20. De Coppi P. Regenerative medicine for congenital malformations. J Pediatr Surg 2013; 48: 273-280.
21. Raya-Rivera AM, Esquiliano D, Fierro-Pastrana R et al. Tissue-engineered autologous vaginal organs in patients: a pilot cohort study. Lancet 2014; 384: 329-336.

Chapter 7

Cloacal malformation patients report similar quality of life as female patients with less complex anorectal malformations.

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Abstract

Purpose Cloacal malformations are the most complex type of anorectal malformation in females. This study aimed to report quality of life (QoL) of patients with a cloacal malformation for the first time in literature.

Materials and Methods Female patients with an anorectal malformation participating in a follow-up program for congenital malformation survivors aged 5 or older were eligible for this study. QoL was assessed with the PedsQL™ 4.0 inventory. Scores of patients with a cloacal malformation (CM) were compared with those of female patients with rectoperineal or rectovestibular fistulas (RP/RV) and with reference data.

Results A total of 59 patients (67% response rate; 13 patients with cloacal malformation) were included, QoL was assessed by patient self-report at median age of 12 years (8-13), and by parent proxy-report at median age of 8 years (5-12). There were no differences between groups regarding the presence of associated anomalies, with also no differences regarding anomalies in the urinary tract (CM vs. RP/RV = 31% vs. 15%, p=0.237). Scores of the cloacal malformations group were similar to those of the comparison group, except the proxy-reported scores on school functioning (60.0 vs. 80.0, p=0.003). Proxy-reported scores of cloacal malformation patients were significantly lower than reference values on total QoL-score, psychosocial health, and emotional and school performance. Patients (irrespective of type of ARM) who suffered from fecal soiling reported significantly lower scores with regard to psychosocial health (71.7 vs. 81.7, p=0.034) and its subscale school performance (65.0 vs. 80.0, p<0.001). QoL-scores reported by cloacal malformation patients did not differ significantly from the reference values of the healthy population. Parents of cloacal malformation patients reported significantly lower total QoL, emotional and school performances, as well as a lower general psychosocial health for their children relative to reference data of healthy children.

Conclusion Patients with cloacal malformations and females with less complex anorectal malformations report similar QoL. Parents of cloacal malformation patients report more problems on several psychosocial domains relative to the healthy reference group. To monitor these matters, long-term follow-up protocols should contain multidisciplinary treatment including periodical assessment of psychosocial wellbeing.

Introduction

In patients born with a cloacal malformation the anus is absent and the rectum, vagina and urethra confluence in one common channel. Cloacal malformations are considered more complex than other types of anorectal malformations (ARM) in females, such as rectoperineal or rectovestibular fistulas.[1] Most ARM patients will undergo multiple surgical procedures in the first years of life, which aim to achieve the best possible bowel function, urological function, and gynecological function. However, the majority of cloacal malformation patients will still suffer from long-term impairments in one or more of these functions.[2] These impairments may have an impact on QoL. On the other hand, a study in patients with ARM – but not including patients with cloacal malformations – found that impairments such as fecal incontinence or constipation had almost no effect on QoL and that psychosocial functioning was more important.[3] In another study by Hartman *et al.,* however, poorer QoL was reported for female patients and for patients suffering from associated congenital anomalies.[4] Thus, as a cloacal malformation obviously occurs in females only, and considering that in up to 88% of cases it is associated with other congenital anomalies[5], there is reason to expect that QoL in the latter patients will be lower than that in female patients with other ARM. We are not aware of studies that have addressed this assumption. With this study, therefore, we aimed to report QoL in patients with cloacal malformations during childhood and adolescence for the first time in literature and to compare outcomes with those in female patients born with a rectoperineal or a rectovestibular fistula. We furthermore compared them with reference values of the general Dutch population.

Methods and materials

All ARM patients treated in our institution (Erasmus MC-Sophia Children's Hospital) are invited to join a prospective, structured follow-up program for congenital malformation survivors.[6,7] The assessment protocol for this program is standard of care at our institution. The Erasmus MC Medical Ethical Review Board (IRB) ruled that the "Medical Research in Human Subjects Act" does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behavior being imposed. Therefore, IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes. Included in the program is a periodical assessment of QoL using proxy-reports from the age of 5 years and additionally self-reports from 8 years onwards. All female ARM patients with a cloacal malformation, or a rectoperineal or rectovestibular fistula aged 5 years and older whose QoL was assessed were eligible. Severe mental or neurological impairment was an exclusion criterion (Fig. 7.1).

QoL was assessed with the PedsQL™ 4.0 inventory[8,9], which was constructed to test health-related QoL in children and adolescents. Validated, age-appropriate versions are available for children aged 5 to 18 years as a parent proxy-report and children/adolescents aged 5 to 25 as patient self-report. The questionnaire assesses both physical health (8 items) and psychosocial health, divided in emotional, social, and school performance (5 items each). All 23 items scored will generate a total QoL-score with a maximum possible score of 100. Parent proxy-reports were completed by the parents at home, self-reports were completed with the help of a psychologist at the outpatient clinic (without parents). If a patient (and/or her parents) had completed the questionnaire more than once, only the latest self- and proxy-reports were used for this study. Data regarding associated anomalies, surgical procedures, and functional outcome such as colorectal function and urinary continence were obtained in the same outpatient clinic with the use of structured interviews. Colorectal function was classified according to the Krickenbeck criteria.[10] Dysfunctional voiding was defined as either urinary incontinence or need for intermittent catheterization. Data were stored and analyzed using SPSS version 21 (SPSS Inc, Chicago, Ill). QoL-scores are expressed as median (IQR) unless otherwise stated. Mann-Whitney U nonparametric tests and one-sample Wilcoxon signed rank tests were used to compare QoL-scores of different types of ARM and to compare these scores with Dutch reference data previously obtained in 74 children aged 7.4 – 18.2 years.[11]

Results

Patient characteristics

Since the introduction of the follow-up program in 1999, 88 female patients with ARM aged five or older were seen at outpatient appointments and met all inclusion criteria. Fifty-nine (67%) of them, and/or their parents, completed at least one PedsQL™ 4.0 (Fig. 7.1). QoL was assessed by patient self-report at a median age of 12 (8-13) years, and by parent proxy-report at a median age of eight (5-12) years. Self-reporting patients in the cloacal malformation group were older than the Rectoperineal/Rectovestibular (RP/RV) comparison group at time of the study (14 [12-19] vs. 12 [8-13] years, p=0.009), ages for the proxy-reporting group were not significantly different from each other (Table 7.1A-B). Associated anatomical anomalies were seen in 32 (54%) of the patients, with no difference between both groups. The most common associated anomalies were (sacro) vertebral anomalies in 16 patients (27%), with no difference between the CM and RP/RV groups (38% vs. 24%, p=0.311), and anomalies in the urinary tract in 11 (19%; CM vs. RP/RV = 31% vs. 15%, p=0.237). No patients were diagnosed with total sacral agenesis. In the CM group length of common channel was missing in 3 patients, for the other 9 mean channel length was 2.0cm (range 1.0-3.0cm). Median (IQR) age at ARM repair

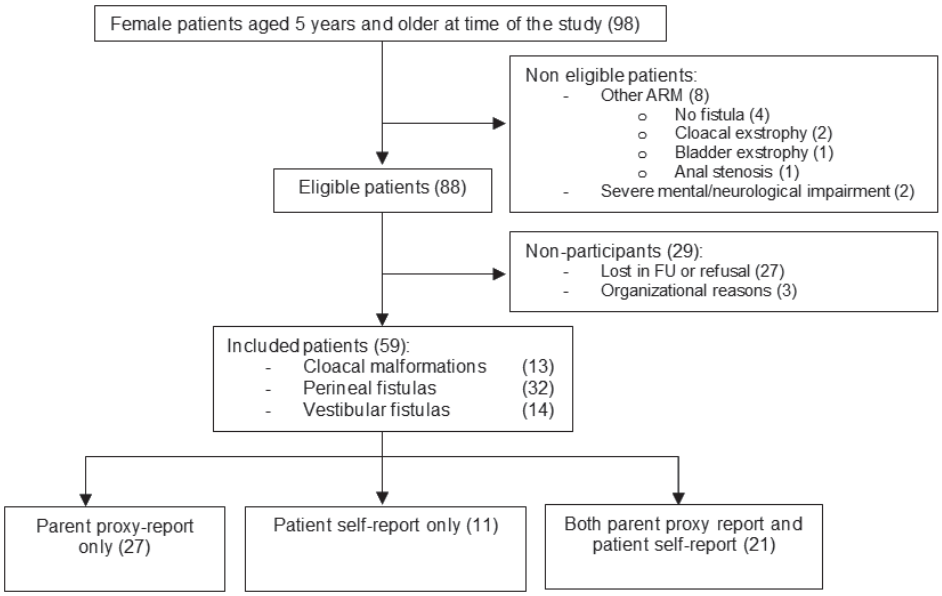

Figure 7.1 *Flow chart of patient inclusion.*

was 10 (4-18) months. Thirty-eight (64%) patients underwent surgical reconstruction by either posterior sagittal approach (42%) or anterior sagittal approach (16%). All but 2 of the cloaca patients underwent a Total Urogenital Mobilization, these 2 underwent a vagino-urethroplasty. A cutback procedure was carried out in three patients with perineal fistulas (5%); and the surgical procedure was unknown in one other patient, who was adopted from China. Twenty-one patients (36%) with rectoperineal fistulas underwent anal dilatations only without surgical correction. At follow-up, fewer patients with cloacal malformations had voluntary bowel movements (VBM) relative to patients with other types of ARM (self-report group: 36% vs. 86; p=0.013; proxy-report group 50% vs. 88%; p=0.031, Table 7.1A-B).

Quality of life questionnaires

Patients with cloacal malformations and patients from the RP/RV comparison group had similar median total (IQR) scores for QoL (81.5 [75.0-87.0] vs. 76.1 [69.0-87.0], p=0.551, Table 7.2A). QoL subscores reported by patients themselves did not differ significantly between CM and RP/RV groups. Parents of patients with a cloacal malformation reported a median total QoL-score of 80.4 (73.4-84.0), which was not different from the RP/RV comparison group (82.1 [69.0-91.6], p=0.554, Table 7.2B). However, parents of patients with a cloacal malformation did report significantly lower scores on school performance than parents of patients with a rectoperineal or a rectovestibular fistula (60.0 [56.3-75.6] vs. 80.0 [68.1-95.0], p=0.003, Table 7.2B).

Table 7.1A. *Clinical characteristics: Patient self-report group (n=32)*

	CM (11)	RP/RV (21)	Total (32)	p-value
Median age (years)	14 (12-19)	12 (8-13)	12 (8-13)	***0.009***
Associated anomalies	6 (55%)	12 (57%)	18 (56%)	1.000
Voluntary bowel movements	4 (36%)	18 (86%)	22 (69%)	***0.013***
Soiling	6 (55%)	7 (33%)	13 (41%)	0.283
Grade 1	3 (27%)	1 (5%)	4 (13%)	
Grade 2	3 (27%)	5 (23%)	8 (25%)	
Grade 3	0 (-%)	1 (5%)	1 (3%)	
Constipation	5 (45%)	11 (52%)	16 (50%)	1.000
Grade 1	0 (-%)	1 (5%)	1 (3%)	
Grade 2	0 (-%)	4 (19%)	4 (13%)	
Grade 3	5 (45%)	6 (28%)	11 (34%)	
Colostomy	3 (27%)	1 (5%)	4 (13%)	0.106
Urological outcome				
Spontaneous voiding	6 (55%)	15/20 (75%)	21/31 (68%)	0.423
Clean intermittent catheterization	2 (18%)	3/20 (15%)	5/31 (16%)	
Incontinence	2 (18%)	2/20 (10%)	4/31 (13%)	
Diversion	1 (9%)	0 (-%)	1/31 (3%)	

Table 7.1B *Clinical characteristics: Parent proxy-report group (n=48)*

	CM (8)	RP/RV (40)	Total (48)	p-value
Median age (years)	12 (6-12)	8 (5-12)	8 (5-12)	0.306
Associated anomalies	4 (50%)	21 (53%)	25 (52%)	1.000
Voluntary bowel movements	4 (50%)	35 (88%)	39 (81%)	***0.031***
Soiling	4 (50%)	18 (45%)	22 (46%)	1.000
Grade 1	1 (12%)	7 (17%)	8 (17%)	
Grade 2	3 (38%)	10 (25%)	13 (27%)	
Grade 3	0 (-%)	1 (3%)	1 (2%)	
Constipation	6 (75%)	20 (50%)	26 (54%)	0.260
Grade 1	0 (-%)	2 (5%)	2 (4%)	
Grade 2	1 (12%)	8 (20%)	9 (19%)	
Grade 3	5 (63%)	10 (25%)	15 (31%)	
Colostomy	1 (12%)	1 (3%)	2 (4%)	0.364
Urological outcome				
Spontaneous voiding	5 (62%)	28/36 (78%)	33/44 (75%)	0.391
Clean intermittent catheterization	3 (38%)	3/36 (8%)	6/44 (14%)	
Incontinence	0 (-%)	5/36 (14%)	5/44 (11%)	

CM *cloacal malformation group;* RP/RV *rectoperineal/rectovestibular group.*

Table 7.2A *Quality of life in female ARM patients by patient self-report.*

	CM (11)	RP/RV (21)	p-value**	Reference values[11]
Total	81.5 (75.0-87.0)	76.1 (69.0-87.0)	0.551	84.2 (10.4)
Physical health	84.4 (75.0-90.6)	81.3 (70.3-92.2)	0.631	88.8 (9.7)
Psychosocial health	78.3 (70.0-86.7)	75.0 (68.3-84.2)	0.604	81.7 (12.2)
Emotional performance	70.0 (65.0-85.0)	75.0 (62.5-82.5)	0.836	78.0 (17.3)
Social performance	85.0 (80.0-95.0)	75.0 (70.0-95.0)	0.388	86.0 (13.4)
School performance	75.0 (65.0-85.0)	75.0 (65.0-85.0)	0.945	81.4 (13.0)

Table 7.2B *Quality of life in female ARM patients by parent proxy-report.*

	CM (8)	RP/RV (40)	p-value**	Reference values[11]
Total	80.4 (73.4-84.0)*	82.1 (69.0-91.6)	0.554	87.6 (11.0)
Physical health	92.2 (90.6-98.4)	89.1 (63.3-99.6)	0.260	93.2 (9.1)
Psychosocial health	71.7 (62.8-78.0)*	80.0 (65.4-91.7)	0.124	84.6 (13.2)
Emotional performance	69.1 (57.5-73.8)*	76.3 (57.5-90.0)	0.258	81.1 (17.4)
Social performance	78.8 (66.3-92.5)	81.3 (70.0-98.8)	0.696	90.3 (14.0)
School performance	60.0 (56.3-75.6)*	80.0 (68.1-95.0)	***0.003***	82.5 (16.3)

CM cloacal malformation group; RP/RV rectoperineal/rectovestibular group.
** Significant difference between cloaca group and reference value, p < 0.05.*
*** p-value describing CM group vs. RP/RV group.*
Data are reported as median (IQR), except for reference values, which are expressed as mean (SD).

Effects of fecal continence and voiding dysfunction on QoL

Patients (irrespective of type of ARM) who suffered from fecal soiling reported significantly lower scores than patients who do not soil with regard to overall psychosocial health (71.7 [65.8-80.0] vs. 81.7 [73.3-86.7], p=0.034) and its subscale school performance (65.0 [57.5-70.0] vs. 80.0 [75.0-90.0], p<0.001). The parents of patients who suffered from dysfunctional voiding (either urinary incontinence or need for intermittent catheterization, irrespective of type of ARM) reported significantly lower scores than the parents of patients without urological disturbances on: total score (68.2 [57.6-80.4] vs. 82.6 [73.9-93.7], p=0.005), overall psychosocial health (61.7 [56.7-76.7] vs. 80.0 [70.0-92.5], p=0.002), emotional performance (55.0 [50.0-70.0 vs. 77.5 [65.0-90.0], p=0.005), and social performance (70.0 [50.0-80.0] vs. 85.0 [75.0-100.0], p=0.004).

Comparison with reference values from the Dutch general population

Reference values were obtained for the Dutch population in a previous study[11] at a mean age of 12.1 years (±3.1), which was not significantly different compared to the cloacal malformation group. Scores obtained from cloacal malformation patients themselves did not differ significantly from the reference values (Table 7.2A). Parents of cloacal malformation patients reported significantly lower total QoL (p=0.012), emotional

(p=0.025) and school performances (p=0.011), as well as a lower general psychosocial health (p=0.012, Table 7.2B) for their children relative to reference data.

Discussion

To date our study is the first assessing QoL in patients with a cloacal malformation in particular, and the results suggest that self-reported QoL may not differ from that of female patients with less complex ARM. Long-term impairments in colorectal, urological, and gynecological function are common in patients with cloacal malformations.[2] The same impairments are known in female patients with other types of ARM, albeit in lower rates.[1] Still, in the present study QoL-scores in cloacal malformation patients were comparable to those of female patients with other types of ARM and to the Dutch reference population, despite the worse functional outcome in the cloacal malformation group. A possible explanation is that in view of the poor long-term prognosis for patients with a cloacal malformation, coping strategies of both parents and patients may have focused on better life quality as was suggested in another study.[12] Furthermore, the majority of cloaca patients in our study were born with short common channel, of whom is known to have better functional outcome compared to patients with long common channels.[13] Parents of patients with a cloacal malformation perceived lower school performance, but this does not hold for the children themselves. The question is whether the proxy-reported scores on school performance reflect actual schooling problems leading to lower educational outcomes, as was suggested in a study of patients with high anorectal malformations[14], or rather parental concern regarding the effect of the child's illness on school performance.[15] Not frequent absence from school, but rather the items concerning 'forgetting things' and 'keeping up with schoolwork' scored below average for the patients with a cloacal malformation. However, psychosocial health-related domains including school performance were significantly lower in patients suffering from fecal soiling (by self-report) and dysfunctional voiding (by proxy-report) in agreement with previous studies.[16-17] Thorough, multidisciplinary follow-up is therefore mandatory in these complex patients in order to optimize the treatment of functional bowel and urinary symptoms (e.g. with the use of bowel management and pelvic floor physiotherapy) and to address their effects on psychosocial wellbeing and school performance. The results reported by proxy in this study suggest that familial involvement in the therapy may be necessary and that family of patients might also benefit from being offered psychosocial support for coping with the child's illness.

Scores on several domains reported by parents were lower than the Dutch reference data, which, however, was not reflected in the patients' self-reported scores. A large study assessing QoL in chronically ill children with gastrointestinal conditions showed

that patients with benign functional conditions (such as chronic constipation) reported a worse QoL than patients with organic disease (such as Crohn's and ulcerative colitis).[18] Total QoL-scores reported by cloacal malformation patients in the present study (80.4-81.5) are close to those of patients with organic disease (75.6-78.0), but tended to be higher than those of patients with benign functional conditions in that study (70.2-70.5). Possibly, this difference is a consequence of the fact that for both ARM and organic disease anatomical and/or inflammatory substrates can be found. In the majority of cases benign functional disorders stay without a clear cause and sometimes even are diagnosed as partially psychological of origin. Conform this, a study by Hartman *et al.* concluded that QoL in ARM patients is more influenced by psychosocial functioning than by functional colorectal outcome.[3] This again emphasizes the need for a low threshold for psychosocial guidance throughout (early) childhood and adolescence in these patients and their parents.

The limited sample size of our study may have influenced outcomes in this assessment and may have increased the risk of type II error. This also contributed to the fact that median age of the cloacal malformation group was higher than in the RP/RV comparison group, which may have influenced the results. Unfortunately, the rarity of cloacal malformations makes the reporting of larger samples difficult. A multi-center assessment similar to our study may show other results, especially when more cloaca patients with long common channels can be included. This study, with a larger group of patients with cloacal malformations, may also make it possible to compare patients from different ages groups with each other, as well as patients with different types of cloaca. For instance, patients with long common channels seem to have poorer functional outcome, as well as patients with severe associated anomalies to sacrum and spine.[13] These patients may, therefore, very well have an impaired QoL compared to patients with short common channels and no associated anomalies. Unfortunately, our series is too small to enable a useful analysis of QoL outcomes in our cloaca patients by length of common channel. Sexual function in relation to QoL was not assessed in this study due to the relatively young age of the sample population. However, this is an important area which requires further assessment in both cloaca and other ARM patients at adult age. It is known that impaired sexual function may lead to severe disturbances in life quality.[19] A future study in a more adult patient population should focus on this matter as well. Lastly, the choice of questionnaire may be questioned. Many different generic questionnaires are available to score QoL. For example, the HAQL is a questionnaire constructed to score disease-specific QoL in patients with Hirschsprung's disease and anorectal malformations.[20] However, we preferred the PedsQL™ 4.0 as it is easier and less time-consuming for patients to complete. Furthermore, the HAQL is not specifically validated for this group of complex patients.

Conclusions

In this study, patients with a cloacal malformation reported similar quality of life as female patients with less complex types of anorectal malformations. Parents of cloacal malformation patients reported comparable QoL compared to parents of RP/RV patients, but lower emotional performance, school performance and psychological health in their child in comparison to data from the Dutch general population. Female patients with ARM reported lower scores when suffering from fecal soiling; lower scores on psychosocial domains were reported by parents of patients suffering from dysfunctional voiding. The long-term assessment of these patients should include a multidisciplinary approach to assess functional problems as well as periodical assessment of the psychosocial well-being of these patients and their parents.

References

1. Levitt MA, Pena A. Anorectal malformations. Orphanet J Rare Dis 2007; 2: 33.
2. Versteegh HP, van Rooij IA, Levitt MA et al. Long-term follow-up of functional outcome in patients with a cloacal malformation: a systematic review. J Pediatr Surg 2013; 48: 2343-2350.
3. Hartman EE, Oort FJ, Aronson DC et al. Critical factors affecting quality of life of adult patients with anorectal malformations or Hirschsprung's disease. Am J Gastroenterol 2004; 99: 907-913.
4. Hartman EE, Oort FJ, Visser MR et al. Explaining change over time in quality of life of adult patients with anorectal malformations or Hirschsprung's disease. Dis Colon Rectum 2006; 49: 96-103.
5. Versteegh HP, Sloots CEJ, de Jong JR et al. Early versus late reconstruction of cloacal malformations: the effects on postoperative complications and long-term colorectal outcome. J Pediatr Surg 2014; 49: 556-559.
6. Gischler SJ, Mazer P, Duivenvoorden HJ et al. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 2009; 44: 1382-1389.
7. van den Hondel D, Sloots CEJ, Gischler SJ et al. Prospective long-term follow up of children with anorectal malformation: growth and development until 5years of age. J Pediatr Surg 2013; 48: 818-825.
8. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999; 37: 126-139.
9. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001; 39: 800-812.
10. Holschneider A, Hutson J, Pena A et al. Preliminary report on the International Conference for the Development of Standards for the Treatment of Anorectal Malformations. J Pediatr Surg 2005; 40: 1521-1526.
11. Bastiaansen D, Koot HM, Bongers IL et al. Measuring quality of life in children referred for psychiatric problems: psychometric properties of the PedsQL 4.0 generic core scales. Qual Life Res 2004; 13: 489-495.
12. Baeten CG, Geerdes BP, Adang EM et al. Anal dynamic graciloplasty in the treatment of intractable fecal incontinence. N Engl Med J 1995; 332: 1600-1605.
13. Levitt MA, Pena A. Cloacal malformations: lessons learned from 490 cases. J Pediatr Surg 2010; 19: 128-138.
14. Hassink EA, Rieu PN, Brugman AT et al. Quality of life after operatively corrected high anorectal malformation: a long-term follow-up study of patients aged 18 years and older. J Pediatr Surg 1994; 29: 773-776.
15. Grano C, Bucci S, Aminoff D et al. Does mothers' perception of social support mediate the relationship between fecal incontinence and quality of life of the child? Pediatr Surg Int 2013; 29: 919-923.
16. Grano C, Aminoff D, Lucidi F et al. Long-term disease-specific quality of life in children and adolescent patients with ARM. J Pediatr Surg 2012; 47: 1317-1322.
17. Grano C, Bucci S, Aminoff D et al. Quality of life in children and adolescents with anorectal malformation. Pediatr Surg Int 2013; 9: 925-930.

18. Varni JW, Bendo CB, Nurko S et al. Health-Related Quality of Life in Pediatric Patients with Functional and Organic Gastrointestinal Diseases. J Pediatr 2015; 166: 85-90.
19. Aslan E, Fynes M. Female sexual dysfunction. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19: 293-305.
20. Hanneman MJ, Sprangers MA, de Mik EL et al. Quality of life in patients with anorectal malformation or Hirschsprung's disease: development of a disease-specific questionnaire. Dis Colon Rectum 2001; 44: 1650-1660.

Chapter 8

General discussion

General discussion

The ancient Greek philosopher and scientist Aristotle documented the first reports of people and animals with aberrant perineal anatomy, dating from the third century B.C.[1] These historical anecdotes in humans mainly comprised treatments such as dilating a dislocated small fistulous rectal opening or the separation of a thin membrane covering the anus indicating a 'low' or slightly less complex anomaly, such as a rectoperineal fistula. The absence of treatment reports of more complex anomalies presumably means that patients suffering from such complex malformations were left untreated and died. The first report of the treatment of a more complex anomaly, in which the rectum could not be found in close proximity of the skin, date from the 18th century.[2] In this report the Scottish surgeon Bell stated that finger guided dissection should be carried out *"till he [the operator] meets faeces"*, and if dissection reached the full length of the operator's finger and no rectal tissue was found a long trocar was to be inserted blindly *"in such a direction as the operator thinks will most probably meet with the gut"* because *"death must undoubtedly ensue if something further is not attempted"*. In the beginning of the 18th century in France the first experiments in creating enterostomies in children were reported by Littre.[3] Over time this resulted in a lifesaving solution for patients with more complex anorectal anomalies, in whom no dislocated rectal opening was apparent. Obstruction of the gastrointestinal tract could now be remedied by creating a colostomy. For girls with a cloacal malformation, however, the creation of a colostomy was only part of the lifesaving remedy. Hydronephrosis and end-stage renal failure were commonly seen in these patients as a consequence of associated anomalies of the urological and gynecological tracts, such as obstruction of the bladder and ureters. This was the reason why until the beginning of the 20th century many girls born with a cloacal malformation did not survive. In the mid-twentieth century it became clear that when a diverting colostomy was created, all other fluid retentions had to be drained by placing vaginal, bladder, and even pelvic kidney drains in order to prevent obstruction of the urinary tract and, thus, prevent renal failure.

In 1965, the pediatric surgeon Louw stated that all congenital malformations of the anus and rectum were generally treated worse than any other anomaly in the newborn.[4] Through efforts of renowned surgeons, such as Stephens, Rehbein, and Peña, this situation changed dramatically.[5] These pioneers in pediatric colorectal surgery introduced structural reconstructive surgery according to anatomical borders and this approach was adopted throughout the world for most anorectal malformations. With the introduction of the posterior sagittal approach by Peña in the 1980s specific modifications for cloacal reconstruction were also introduced. This resulted in an increased number of documented cases and better reports presenting outcome in patients with cloacal

malformation.[6, 7] However, it was only after the so-called Krickenbeck meeting and the introduction of the Krickenbeck classification for anorectal malformations that terms such as 'high' and 'low' anomalies were abandoned and separate types of anorectal anomalies were reported more commonly.[8] Within the wide spectrum of anorectal malformations cloacal malformations are generally marked as the most complex type. Still, it must be noted that no particular reconstructive surgery for any type of anorectal malformation can be assumed to be standard or easy.

Surgical techniques for cloacal repair were well established during the period from 1982 to 1997, but the technological evolution in the field of surgery for cloacal malformations has developed further ever since. In the early years of the posterior sagittal approach for the reconstruction of anorectal malformations the posterior sagittal anorecto vagino urethroplasty (PSARVUP, Fig. 1.6) was the procedure of first choice for most surgeons when operating on a patient with a cloacal malformation.[6] This preference changed after 1997, with the introduction by Peña of the total urogenital mobilization (TUM).[7] In this new approach only the rectum was dissected from the common channel, leaving a urogenital sinus that then needed *en bloc* mobilization to make both urethra and vaginal introitus reach the perineum (Fig. 1.7). Meticulous dissection and division of the urogenital sinus to separate the vagina from the urethra was no longer necessary and cosmetic results were reported to be better than those obtained with the PSARVUP. The major concerns to this technique came from pediatric urologists. With the *en bloc* mobilization of the vagina and urethra, the bladder neck may be placed just low in the pelvic floor resulting in urinary incontinence. In Chapter 4 of this thesis we showed, however, that urological results after PSARVUP and TUM procedures were comparable. Although sample size was small in this study and its nature was retrospective, to date this is the first study to address this subject. A larger, international, and prospective assessment regarding outcomes in cloacal malformation patients may add information to our findings, but until then it seems that both procedures are equally adequate in preserving bladder function and urinary continence in these patients.

In the more recent years other techniques and procedures have been suggested, such as the use of laparoscopy, as well as an anterior transpubic approach for the reoperation of patients with a cloacal malformation who have a persistent urogenital sinus.[9,10] Although the laparoscopic procedure as presented for cloacal malformation surgery had excellent short-term postoperative results, this procedure only comprised correction of the rectal fistula.[10] The urogenital stage of the cloacal reconstruction was conducted in a separate, later stage via a perineal procedure. Major limitation of this new procedure therefore seems to be the need for a second surgical procedure requiring general anesthetics. The transpubic approach has been reported only in case of reoperation for cloacal malfor-

mation reconstruction.[9] The authors reported good results in the five patients operated on, but acknowledged that the procedure was not to be preferred over the established procedures in case of a primary reconstruction. In their series postoperative complications as a direct consequence of the transpubic route were seen in 3 of 42 patients.

Besides surgical management, other factors, such as prenatal imaging (and therefore prenatal diagnosis) and perioperative hospital care, have been improved significantly over the past decades and have been proven of additional use in the accurate diagnosis of anorectal malformation.[11-14] Unfortunately, all these developments have not been able to prevent impairments in long-term functional outcomes of patients with a cloacal malformation. With impaired colorectal outcome (such as fecal incontinence or severe constipation) in up to 76%, impaired urological outcome in up to 31% (urinary incontinence or need for catheterization), and problems with reproductive function in up to 45% for example suffering from amenorrhea, it is clear that only a minority of these patients seem to be without serious sequelae. It should not be left unmentioned, of course, that associated anatomical malformations are seen in 88% of cases. Some of these, such as asymptomatic cardiac anomalies, may have only limited implications for day-to-day life, although clear evidence supporting this supposition is lacking. Other anomalies, such as major cardiac, limb, spinal, or renal anomalies, will probably have an impact, not only in the neonatal period but also in later life. It seems legitimate to claim that the conditions of these patients are in fact extremely complex and within the range of anorectal malformations among the most complex of all both in terms of neonatal care as well as long-term follow up.

The improved surgical technique brings the need to adjust other factors in order to reach better functional outcome. It has been realized that a surgeon is required to perform a certain minimum number of complex (if not all) surgical procedures annually to gain enough experience for that particular procedure. The same may be true for the rest of the team involved in the treatment, e.g. urologist, gynecologist, specialist nurses. With the current incidence of cloacal malformation, which is approximately 1 in every 50,000 newborns, 3 or 4 new cases a year can be expected in the Netherlands. As there are currently five pediatric surgery facilities in the Netherlands where these patients can be treated, specialized pediatric surgeons in these centers will probably not even see one new case every year. Gaining experience in these complex procedures, thus, is possible for surgeons in the Netherlands only by visiting one of the major referral centers abroad or special workshops. And for that matter, the question whether we really need 5 separate centers treating these patients in such a small country such as the Netherlands remains to be answered by heads of departments and policymakers. The simultaneous development of Centers of Expertise for Rare Diseases, imposed by

the European Committee and adopted by all university hospitals in the Netherlands, may help make the right choice in the reorganization of care for these patients. These centers of expertise have to fulfill criteria set by independent committees that evaluate items such as basic research, clinical output, the organization of multidisciplinary teams, facilities, long-term follow up, and transition of adolescents to adult medical care.

Long-term follow up seems to be an excellent strategy to assess and treat the functional impairments seen in patients with congenital anomalies. In the Erasmus Medical Center – Sophia Children's Hospital all patients with congenital anomalies, including anorectal malformations, are invited to participate in a structural long-term follow-up program.[15] For girls with a cloacal malformation this involves periodical appointments up to the age of 18 years that among other things will cover surgical, urological, and physical and mental development aspects. If thought necessary patients will transition to a combined pediatric/adult outpatient clinic after the age of 18 years. The visiting schedule as organized now in our clinic is shown in Table 8.1.

This thesis made clear that patients with a cloacal malformation are not only surgical, but also urological and gynecological patients. Indeed, anatomical anomalies of the gynecological tract, such as duplicate uteruses or uterus septation, were found in up to 64% of cases (Fig 8.1). As is shown is chapters 2 and 4, several of the patients involved will suffer from abnormal menstruations and up to 15-38% will even undergo further surgery in order to relieve obstructed flow of menstrual blood. It would be worthwhile, therefore, to add gynecological consults to the long-term follow-up program in for patients with a cloacal malformation in particular. Patients with a cloacal malformation should be seen by a gynecologist at least at the age of 12 years as menarche seems to be around the age of 11-13 years according to literature.[16,17] Still we would recommend referral for gynecological consult even earlier if signs of puberty become noticeable at younger age or whenever non-colorectal or non-urological abdominal symptoms arise during childhood. A gynecological consult before the first menstruation could serve as a counseling for both parents and patients informing them on possible complications that may arise. This consult may also be used to assess the risk for any possible problems

Table 8.1 *Current follow up moments for all patients with anorectal malformations*

	6 months	1 year	2 years	5 years	8 years	12 years	17 years
Pediatrician	X	X	X	X	X	X	X
Pediatric surgeon	X	X	X	X	X	X	X
Clinical geneticist	X						X
Psychologist			X	X	X	X	X
Physiotherapist				X	X	X	

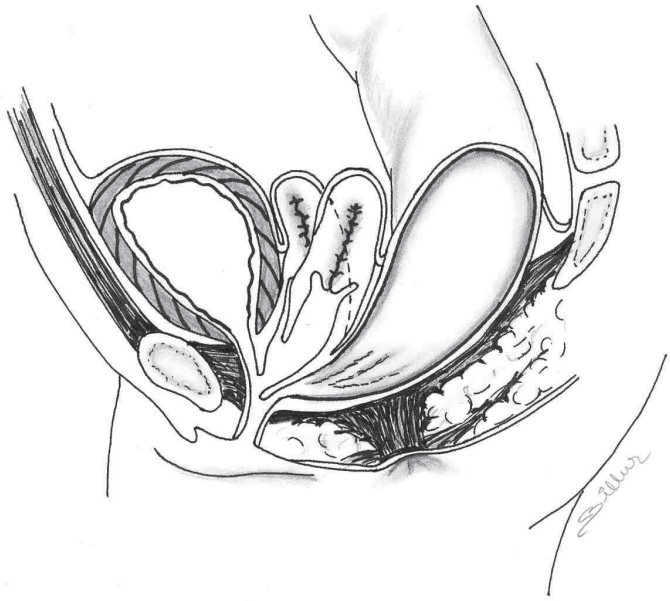

Figure 8.1 *A cloacal malformation with a duplicature of the Müllerian structures (uterus didelphys), present in up to 64% of the cloaca patients.*

related to the menstrual using a physical gynecological examination as well as ultrasound studies. A visiting schedule for such an extended follow-up program for patients with a cloacal malformation is proposed in Table 8.2 for the fields of medicine addressed in this thesis as well as fields that lie outside the focus of this thesis but we feel are of great importance in the follow-up of these complex patients. An additional follow-up moment is scheduled at the age of 3 years in this extended follow-up, which could serve as an evaluation of both urinary and fecal continence and assess the possible need for continence training. There may, however, be a downside to an extended follow-up

Table 8.2 *Extended follow-up program for patients with a cloacal malformation.*

	6 months	1 year	2 years	3 years	4 years	5 years	8 years	12 years	15 years	18 years
Pediatric surgeon	X	X	X	X	X	X	X	X	X*	X*
Urologist	X	X	X	X	X	X	X	X	X*	X*
Pediatrician	X	X	X		X	X				
Clinical geneticist	X									
Psychologist			X		X	X	X	X	X	X
Physiotherapist						X	X	X		
Gynecologist								X	X*	X*
Sexologist										X**

Appointment scheme and appropriate specialists may vary according to specific cases.
Transition to appropriate adult specialists. When indicated.*

program. Throughout this thesis, one of the main limitations of the studies comprised the small sample sizes. On the one hand this is due to the rarity of the condition. On the other hand, a number of parents of cloacal malformation patients seemed reluctant to let their child participate in the study. This was mainly the case if participation involved an additional hospital visit. Thus it is not unreasonable to assume that adding gynecological consults to the follow-up program of cloacal malformation patients may increase the burden experienced by both parents and patients. A recent Canadian study assessing the burden of care compared between outpatient visits and telemedicine indicated that parents preferred the latter, possibly because this is associated with lower costs.[18] This is quite different for parents in the Netherlands as travel distances to the hospital – and related costs – in this small country obviously are much shorter than in the Canadian situation. Furthermore, the potential burden of additional hospital visits may be alleviated by combining several appointments in one hospital visit.

With the extension of follow-up appointments in patients with cloacal malformations, as is proposed in Table 8.2, we feel that these patients should undergo transition to adult medical services at some point during adolescence. Unlike patients with less complex congenital anomalies, for patients with cloacal malformations the question should not be *if* but rather *when* these patients are transferred to the medical guidance of adult specialists, especially given the fact that complications and functional disturbances are common in these patients even as adults.[19] Who the appropriate specialist may be to perform long-term follow up in these patients is another point of debate, however, a study regarding this matter indicated that a substantial part of the patients fails to participate further adult follow-up after transition because of a lack of knowledge among adult specialists.[20] A collaboration between pediatric specialists and dedicated adults peers may be the ideal way to organize such transition, and is currently the standard of care for surgical transition within the Erasmus Medical Center.[21] Whether or not this should involve surgery, urology and gynecology in separate appointments or rather different specialists combined within one outpatient visit is to be discussed.

Colorectal and urological functions are the most common reported outcomes in studies on outcome in patients with a cloacal malformation. In our nationwide assessment colorectal function was severely impaired in the majority of patients with only 24% being capable of voluntary bowel movements and up to 60% of patients requiring enemas or rectal washouts to treat constipation. Regarding urological function the majority of patients were able to void spontaneously (69%), although one third of the patients could empty the bladder sufficiently only with intermittent catheterization. We also assessed gynecological outcome, which we considered of major importance in patients with a cloacal malformation. It appeared that only 55% of the post puberty patients

had normal menstruations and that 15% of the patients urgently needed surgery for an obstructed menstrual flow. Apart from functional outcome, quality of life (QoL) is an important outcome within any group of patients. Several strategies are available to measure QoL including questionnaires for self-report or report-by-proxy (e.g. parents scoring the QoL of their children). We performed a study in which we administered one of those widely used and validated questionnaires to assess QoL in female children and adolescents with anorectal malformations. This study indicated that, although patients with cloacal malformation suffered from more functional impairments, their QoL did not differ from that of female patients with less complex anorectal malformations. Furthermore, results showed that functional impairment such as fecal soiling and dysfunctional voiding led to lower reported scores for psychosocial health and its determinants. The long-term follow up of patients with a cloacal malformation therefore should also comprise the periodical evaluation of psychosocial health. More emphasis should be placed on school performance throughout childhood and adolescence and the likelihood of it being influenced by functional impairment.

Recommendations

In this thesis we studied the surgical, postoperative, and long-term outcomes in patients with a cloacal malformation in the Netherlands. The results of these studies led us to propose the following recommendations for the near future:

- Reconstructive surgery of cloacal malformations in centers with limited experience is best conducted after the first six months of life, but this age limit may be lowered with increasing experience with these types of surgery.
- Gaining experience with reconstructive surgery of cloacal malformation is essential and could be achieved by creating appropriate sufficient number of centers of expertise as well as international collaborations, such as the ARM-Net.[22,23]
- Multidisciplinary follow up of patients with a cloacal malformation is essential, and should comprise surgical, urological, gynecological, pediatric, and psychological and psychosocial assessment (Table 8.2).
- With the extension of follow-up program of patients with complex congenital malformations such as cloacal malformations centers of expertise should also organize transition of care to adult specialists for these patients. Ideal transition most presumably involves a collaboration of both pediatric and dedicated adult specialists.

Future perspectives

Long-term follow-up

The Long-term outcome of patients with a cloacal malformation may benefit from the recommendations as proposed above; an extended follow up program – including periodical gynecological evaluation – may lead to an earlier recognition and treatment of clinical impairments, and thereby obviate certain long-term complications, such as need for emergency laparotomy in case of hematometra. Setting up international collaborations of pediatric surgery departments will allow to create large, prospective databases as well as platforms for dedicated pediatric surgeons providing knowledge sharing and consulting expert panels on clinical challenges, which may lead to new insights in the treatment of rare congenital malformations, such as cloacal malformations. These new insights are likely to lead to improved clinical outcome.

Centralization of care

In a small, although densely populated country like the Netherlands some rare conditions requiring very specific treatments should be centralized. This has already been done for children born with congenital diaphragmatic hernia. Congenital diaphragmatic hernia is very rare with an incidence of 2.3 in every 10,000 newborns, but is even a more common condition than cloacal malformation.[24] This is the more reason to centralize care for patients with cloacal malformation. It is of course inevitable that the appointed centers of expertise for pediatric colorectal conditions should take care of the centralized surgical care and perhaps even long-term follow-up of patients with cloacal malformations in the Netherlands.

Genetics

Although studies regarding genetics did not reveal any clear link to specific candidate genes in the etiology of anorectal malformation, let alone cloacal malformation in particular[25], future studies with the use of cheaper and more extensive gene assessment, such as whole genome sequencing, could be useful in studying anorectal malformation etiology.[26] This could in particular be true for specific congenital conditions in combination with other specific associated anomalies.[27]

Surgical and reconstructive progressions

The evolution in surgical technology will continue. With the dramatically increased application of laparoscopic and robot-guided surgical techniques it is likely that these techniques will find more and more recognition in the field of pediatric surgery as well. Also, the use of tissue engineered organs has been studied and this was proven feasible in patients with congenital anomalies of the pelvic organs, such as vaginal agenesis

in patients with Mayer-Rokitansky-Küster-Hauser syndrome and bladder dysfunction in patients with a myelomeningocele.[28,29] In another study women with obstetric anal sphincter trauma were injected with autologous muscle-cells in the external anal sphincter.[30] Results indicated an improvement in quality of life and incontinence scores. An animal study in which tissue engineered human internal sphincter constructs were implanted in rats reported promising results regarding complications and colorectal function.[31] These new techniques may become of use in the treatment of patients with complex congenital malformations of the pelvic floor and pelvic organs – in combination with the current techniques for anorectal malformation surgery – and are likely to improve the postoperative functional results in patients with a cloacal malformation.

References

1. Peck AL. Aristotle. Generation of Animals. Harvard University Press: Cambridge, Mass, 1953: 444-447.
2. Bell B. A system of surgery, 3rd edition. Edinburgh 1787: 275-282.
3. Littre A. Diverses observations anatomiques. Paris, histoire de l'academie royale de science, 1710: 36-37.
4. Louw JH. Congenital Abnormalities of the Rectum and Anus. Curr Probl Surg 1965: 1-64.
5. Holschneider AM, Jesch NK, Stragholz E et al. Surgical methods for anorectal malformations from Rehbein to Pena--critical assessment of score systems and proposal for a new classification. Eur J Pediatr Surg 2002; 12: 73-82.
6. Pena A, Devries PA. Posterior sagittal anorectoplasty: important technical considerations and new applications. J Pediatr Surg 1982; 17: 796-811.
7. Pena A. Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg 1997; 32: 263-267.
8. Holschneider A, Hutson J, Pena A et al. Preliminary report on the international conference for the development of standards for the treatment of anorectal malformations. Journal of Pediatric Surgery 2005; 40: 1521-1526..
9. Pena A, Bischoff A, Levitt MA. The transpubic approach for the correction of complex anorectal and urogenital malformations. J Pediatr Surg 2011; 46: 2316-2320.
10. Liem NT, Quynh TA. Laparoscopic rectal pull-through for persistent cloaca: an easier approach for a complex anomaly. J Pediatr Surg 2012; 47: 815-818.
11. Calvo-Garcia MA, Kline-Fath BM, Levitt MA et al. Fetal MRI clues to diagnose cloacal malformations. Pediatr Radiol 2011; 41: 1117-1128.
12. Burd RS, Mellender SJ, Tobias JD. Neonatal and childhood perioperative considerations. Surg Clin North Am 2006; 86: 227-247.
13. Pena A, Hong A. Advances in the management of anorectal malformations. Am J Surg 2000; 180: 370-376.
14. McCann ME, Soriano SG. Progress in anesthesia and management of the newborn surgical patient. Semin Pediatr Surg 2014; 23: 244-248.
15. Gischler SJ, Mazer P, Duivenvoorden HJ et al. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 2009; 44: 1382-1389.
16. Breech, L. Gynecologic concerns in patients with anorectal malformations. Semin Pediatr Surg 2010; 19: 139-145.
17. Juul A, Teilmann G, Scheike T et al. Pubertal development in Danish children: comparison of recent European and US data. Int J Androl 2006; 29: 247-255.
18. Bator EX, Gleason JM, Lorenzo AJ et al. The burden of attending a pediatric surgical clinic and family preferences toward telemedicine. J Pediatr Surg 2015: *In press*.
19. Schmidt D, Jenetzky E, Zwink N et al. Postoperative complications in adults with anorectal malformation: a need for transition. German Network for Congenital Uro-REctal Malformations (CURE-Net). Pediatr Surg Int 2012; 28: 793-795.

20. Durkin ET, Zurakowski D, Rangel SJ et al. Passing the baton: The pediatric surgical perspective on transition. J Pediatr Surg 2015; 50: 1196-200.

21. Muise ED, Cowles RA. Transition of care in pediatric surgical patients with complex gastrointestinal disease. Semin Pediatr Surg 2015; 24: 65-68.

22. van der Steeg HJ, Schmiedeke E, Bagolan P et al. European consensus meeting of ARM-Net members concerning diagnosis and early management of newborns with anorectal malformations. Tech Coloproctol 2015; 19: 181-185.

23. Schmiedeke E, de Blaauw I, Lacher M et al. Towards the perfect ARM center: the European Union's criteria for centers of expertise and their implementation in the member states. A report from the ARM-Net. Pediatr Surg Int 2015; *In press*.

24. McGivern MR, Best KE, Rankin J et al. Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study. Arch Dis Child Fetal Neonatal Ed 2015; 100: 137-144.

25. Wijers CH, van Rooij IA, Marcelis CL et al. Genetic and nongenetic etiology of nonsyndromic anorectal malformations: a systematic review. Birth Defects Res C Embryo Today 2014; 102: 382-400.

26. Bamshad MJ, Ng SB, Bigham AW et al. Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet 2011; 12: 745-755.

27. van de Putte R, Wijers CH, de Blaauw I et al. Sequencing of the DKK1 gene in patients with anorectal malformations and hypospadias. Eur J Pediatr 2015; 174: 583-587.

28. Raya-Rivera AM, Esquiliano D, Fierro-Pastrana R et al. Tissue-engineered autologous vaginal organs in patients: a pilot cohort study. Lancet 2014; 384: 329-336.

29. Atala A, Bauer SB, Soker S et al. Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet 2006; 367: 1241-1246.

30. Frudinger A, Kölle D, Schwaiger W et al. Muscle-derived cell injection to treat anal incontinence due to obstetric trauma: pilot study with 1 year follow-up. Gut 2010; 59: 55-61.

31. Raghavan S, Miyasaka EA, Gilmont RR et al. Perianal implantation of bioengineered human internal anal sphincter constructs intrinsically innervated with human neural progenitor cells. Surgery 2014; 155: 668-674.

Chapter 9

Summary / Samenvatting

Summary

This thesis highlights the current issues regarding care for patients with cloacal malformations. Cloacal malformations are rare congenital anomalies and patients suffering from these malformations have only scarcely been assessed in a thorough fashion. Aim of this thesis was to assess the postoperative and long-term courses. We aimed for an improvement of the long-term management of cloacal malformation patients.

In **Chapter 1** a general introduction to this thesis elaborated the differences between normal anorectal anatomy and the several types of anorectal malformation, including different types of cloacal malformation. The current thoughts on embryological development of such malformation is given. Furthermore, the neonatal management for cloacal malformation patients was briefly highlighted, since this thesis mainly focused on the postoperative and long-term eras. This neonatal management mainly comprises the creation of a colostomy, placing drains in the urinary and genital tracts, and assess the presence of associated anatomical anomalies. In short, an aim for this thesis was stated at the end of this chapter.

Chapter 2 served as a systematic review on functional outcome in patients with cloacal malformations. We focused on functional outcome, which was described as colorectal function, such as fecal incontinence or constipation, urological function (urinary incontinence, need for catheterization), and gynecological function in terms of reproductive function and sexual function. This review revealed that disturbances in all of these 3 systems are common in patients with cloacal malformations, with voluntary bowel movements being present in 57% of the patients and spontaneous voiding in 46%. Gynecological outcome in these patients is only scarcely reported and disturbances occurring in the gynecological tract may be underdiagnosed in clinic.

In the two following chapters the results of a nationwide retrospective cohort study were presented. This study aimed to assess functional outcome in all cloacal malformation patients treated in the Netherlands from 1985 to 2009. In **Chapter 3** first the postoperative complications and colorectal outcomes were presented and were used to assess ideal age to perform the reconstructive surgery. Postoperative complications were seen in 35% of the patients, voluntary bowel movements in 24%, fecal soiling in 33%, and severe constipation in 60% of the patients. Although wound complications were more common in patients operated on before 6 months of age, these patients had comparable overall complication rates and long-term colorectal function outcomes as patients operated on after the first 6 months. It is concluded in this chapter that the

surgical correction of cloacal malformations is best conducted after the first 6 months, although ideal age may become younger with the increase of experience.

In **Chapter 4** the same nationwide cohort was used to study the effects of the two different surgical techniques (Posterior Sagittal AnoRecto Vagino UrethroPlasty and Total Urogenital Mobilization) used for cloacal malformation surgery on urological and gynecological outcome. Where the Total Urogenital Mobilization was previously suspected to lead to higher incidences of urological impairments, this assessment showed that there were no differences between the group operated on with the vagino urethroplasty and the group of patients who underwent the Total Urogenital Mobilization. Gynecological impairments, such as amenorrhea and the need for additional gynecological surgery, are common in patients with cloacal malformations. Gynecological follow-up should therefore be mandatory in all these patients and should start from the age of 11-13 years or younger when signs of menarche arise.

Chapter 5 continued with assessing bladder function in patients with cloacal malformations and other anorectal malformations. In order to find out if the posterior sagittal surgical technique (as used in all types of ARM) is potentially harmful for the preservation of bladder function, we compared bladder function as assessed by video urodynamic studies both before and after the posterior sagittal anorectal reconstruction. These urodynamic studies revealed significant changes in bladder capacity and emptying efficiency after surgery. However, these changes did not lead to changes in clinical bladder function as the majority of patients had unchanged bladder function after surgery compared to the urodynamic study conducted preoperatively. It was concluded that the posterior sagittal technique is an adequate technique for the preservation of bladder function.

Chapter 6 reports on the current medical literature that presents data on postoperative complications after the surgical cloaca repair. This review showed that postoperative complications are frequently seen in patients with cloacal malformations. Rather than appointing a direct cause of this high incidence, we advised the implementation of a thorough registry for postoperative complications. An increase of information regarding complications may lead to a better understanding as well as a possible prevention.

Besides the functional outcomes generally reported in patients with congenital disorders, assessment of quality of life is of more and more importance in the follow up of patients with chronic conditions. In **Chapter 7** we assessed quality of life as reported by patients with cloacal malformations and their parents. As cloacal malformations are generally classified as being more complex conditions than other anorectal malforma-

tions, such as rectoperineal and rectovestibular fistulas, a group of female patients with these conditions served as a comparison group. Patients with cloacal malformations and females with less complex anorectal malformations reported similar quality of life. When comparing quality of life as reported for the cloaca group with reference values of the healthy population parents of cloacal malformation patients reported more problems on several psychosocial domains, such as school and emotional performance. To monitor these matters, long-term follow-up protocols should contain multidisciplinary treatment including periodical assessment of psychosocial wellbeing. Appropriate and early intervention may lead to improved outcome.

In the general discussion of this thesis, **Chapter 8**, a brief summary of all previous chapters is given. Main conclusions, as well as points of discussion and limitations to the studies are elaborated. Overall it is concluded that a majority of the patients with cloacal malformations suffer from impairments in one or more of the tracts involved in this condition. Current surgical techniques, although not leading to perfect outcome, do not seem to do any further harm to bladder function. Quality of life as reported by patients with cloacal malformations was similar compared to that reported by female patients with less complex anorectal malformations. The further evolution of surgical techniques is one way how long-term outcomes may improve in these patients, however, these techniques – such as the use of tissue engineered organs – will have to be developed further in order to be used as a standard of treatment in patients with congenital organ anomalies. Further recommendations that arise from this thesis are:

- Reconstructive surgery of cloacal malformations is best conducted after the first six months of age in centers with limited experience, although when experience increases age at surgery may become lower.
- Gaining experience in the surgery of cloacal malformation is essential and could be achieved by creating an appropriate number of centers of expertise and international collaborations, such as the ARM-Net.
- Multidisciplinary follow-up of patients with cloacal malformations is essential, and should comprise surgical, urological, gynecological, and psychological and psychosocial involvement (Table 8.2).
- With the extension of follow-up of patients with complex congenital malformations such as cloacal malformations centers of expertise should also organize transition of care to adult specialists for these patients. Ideal transition most presumably involves a collaboration of pediatric specialists and dedicated adult peers.

Samenvatting

Dit proefschrift belicht de huidige gang van zaken omtrent de zorg voor patiënten die geboren zijn met een cloacale malformatie. Bij cloacale malformaties gaat het om zeer zeldzame aangeboren afwijkingen, patiënten met deze aandoening zijn slechts zelden grondig onder loep genomen in het kader van wetenschappelijk onderzoek. Het doel van dit proefschrift was dan ook om de postoperatieve uitkomsten en de lange termijn zorg voor deze patiënten in kaart te brengen. De conclusies van dit proefschrift zouden moeten leiden naar een verbetering in de lange termijn follow-up van patiënten met een cloacale malformatie. Daarnaast hopen wij dat een zorgvuldige analyse als deze als voorbeeld kan dienen voor andere patiëntengroepen waarbij het gaat om zeldzame aangeboren afwijkingen.

Hoofdstuk 1 van dit proefschrift is een algemene introductie tot het onderwerp. De normale en – in het geval van anorectale malformaties – afwijkende anatomie wordt besproken. Ook is in dit hoofdstuk kort ingegaan op de huidige gedachten omtrent de embryologische ontwikkeling van deze aandoeningen. Daarnaast is kort uiteengezet hoe het huidige neonatale beleid is bij patiënten met een cloacale malformatie, namelijk het belang van het aanleggen van een colostoma en het inbrengen van drains in de urinewegen en de gynecologische organen waar nodig.

In **Hoofdstuk 2** worden de uitkomsten van een systematische review naar de huidige wetenschappelijke literatuur over de functionele uitkomsten van patiënten met een cloacale malformatie gepresenteerd. Bij het uitvoeren van deze review hebben we ons gericht op de functionele uitkomsten: colorectale functie (bijv. incontinentie voor ontlasting), urologische uitkomsten (incontinentie voor urine, noodzaak tot catheteriseren) en gynaecologische functie (reproductieve en sexuele uitkomsten). Dit onderzoek toonde aan dat in alle drie de uitkomsten veel problemen voorkomen bij patiënten met een cloacale malformatie. Daarnaast was het aantal studies dat zich heeft gericht op de gynaecologische functie in deze patiënten erg gering, wat erop zou kunnen duiden dat dit een probleem is waar nog te weinig aandacht voor is geweest in deze patiënten.

De volgende twee hoofdstukken beschrijven de uitkomsten van een nationale database, die als doel had de functionele uitkomsten van alle patiënten die in Nederland zijn geboren met een cloacale malformatie in de periode tussen 1985 en 2009 te verzamelen. In **Hoofdstuk 3** worden allereerst de postoperatieve complicaties en de colorectale functionele uitkomsten beschreven. Om de ideale leeftijd om deze kinderen te opereren vast te stellen, werden patiënten die op jonge leeftijd (<6maanden) zijn geopereerd vergeleken met patiënten die op iets latere leeftijd zijn geopereerd. Hieruit

bleek dat zowel complicaties als problemen met colorectale functie vaak voorkomen bij deze patiënten, echter dat het erop lijkt dat de leeftijd van operatie hier maar weinig invloed op heeft. Wel werd geconcludeerd dat kinderen in de Nederlandse situatie bij een operatie na de eerste zes maanden wellicht iets minder kans hebben op het oplopen van postoperatieve wondcomplicaties.

In **Hoofdstuk 4** werd de eerder genoemde nationale database gebruikt om te onderzoeken of de twee verschillende operatietechnieken die gebruikt worden bij patiënten met een cloacale malformatie invloed hebben op de urologische en gynaecologische uitkomsten. De Totale Urogenitale Mobilisatie-techniek werd in het verleden in verband gebracht met postoperatieve urologische problemen. Onze gegevens toonden aan dat er wat betreft urologische en gynaecologische uitkomsten geen verschil zat tussen de patiënten die de Totale Urogenitale Mobilisatie-techniek hadden ondergaan ten opzichte van de patiënten die een Vaginourethroplastiek hadden ondergaan. Ook bleek uit dit hoofdstuk dat gynaecologische problemen, zoals amenorroe en de noodzaak voor gynaecologische operaties, niet zeldzaam zijn in deze patiëntengroep. Derhalve concludeerden wij dat regelmatige gynaecologische controles onderdeel uit moeten maken bij patiënten die geboren zijn met een cloacale malformatie.

Vervolgens werd in **Hoofdstuk 5** nog dieper ingegaan op de mogelijke invloed van de operatie op de blaasfunctie. Om te onderzoeken of de posterieure sagittale operatietechniek (zoals die gebruikt wordt voor alle typen anorectale malformaties) mogelijk zou kunnen leiden tot een vermindering van de blaasfunctie werd de blaasfunctie zowel voor als na de operatie in groep patiënten met anorectale malformaties vergeleken. De blaasfunctie werd in kaart gebracht met behulp van Video Urodynamisch Onderzoek. Deze urodynamische studies toonden aan dat zowel blaascapaciteit als blaasledigingsefficiëntie wel degelijk een significante verandering laten zien na de operatie. Echter wanneer de uitkomsten van de onderzoeken worden geclassificeerd blijkt dat deze veranderingen in de meerderheid van de patiënten niet leidt tot een veranderde blaasfunctie.

Naast de functionele uitkomsten, zoals die vaak gerapporteerd worden in studies naar patiënten met functionele en aangeboren afwijkingen, wordt er steeds vaker ook onderzoek gedaan naar de kwaliteit van leven van dit soort patiënten. In **Hoofdstuk 7** is de kwaliteit van leven onderzocht zoals die door patiënten met een cloacale malformatie en hun ouders wordt gerapporteerd. Aangezien cloacale malformaties doorgaans worden gezien als de meest complexe anorectale malformatie, zijn de uitkomsten op het gebied van kwaliteit van leven vergeleken met een groep vrouwelijke patiënten met 'minder' complexe anorectale malformaties (rectoperineale fistels en rectovestibulaire fistels).

Beide patiëntengroepen rapporteren een vergelijkbare kwaliteit van leven. Wanneer er vergeleken wordt met referentiewaarden van de kwaliteit van leven zoals deze gescoord zijn door gezonde kinderen (en hun ouders) van vergelijkbare leeftijd dan blijkt dat de ouders van patiënten met een cloacale malformatie meer problemen aangeven op het gebied van kwaliteit van leven en specifiek op de verschillende psychosociale uitkomsten. Om deze eventuele moeilijkheden goed te onderzoeken en zo nodig te behandelen is een periodieke psychologische controle van toegevoegde waarde in de follow-up van patiënten met een cloacale malformatie. Eventuele problemen zouden dan vroegtijdig opgespoord en zo nodig behandeld kunnen worden, wat tot betere uitkomsten zou kunnen leiden.

In de algemene discussie van dit proefschrift, **Hoofdstuk 8**, worden alle voorgaande hoofdstukken kort samengevat. De conclusies van deze hoofdstukken, alsmede de discussiepunten die door de studies worden opgeroepen en de beperkingen die de verschillende studies met zich mee hebben gebracht worden kort uiteengezet. Over het algemeen kan geconcludeerd worden dat het merendeel van de patiënten die geboren is met een cloacale malformatie op de lange termijn nog veel beperkingen ondervindt in één of meer van de onderzochte functies. De huidige chirurgische technieken lijken, alhoewel ze dus niet tot perfecte resultaten leiden, niet te leiden tot extra schade aan de blaasfunctie. De kwaliteit van leven zoals gerapporteerd door patiënten met een cloacale malformatie is gelijkwaardig aan die gerapporteerd door vrouwelijke patiënten met een minder complexe anorectale malformatie. De ontwikkeling van nieuwe chirurgische technieken is één manier waarop de uitkomsten in deze patiëntengroep zouden kunnen verbeteren. Daarbij moet echter gezegd worden dat deze technieken, zoals het gebruik van in het laboratorium gecreëerde organen, nog verder ontwikkeld moeten worden voordat ze als standaardbehandeling in aanmerkingen komen voor patiënten met aangeboren orgaanafwijkingen. Overige aanbevelingen die voortkomen uit dit proefschrift zijn:

- De definitieve chirurgie ter correctie van een cloacale malformatie kan het best na de eerste zes maanden worden uitgevoerd in centra met een beperkte ervaring op het gebied van cloacale malformatie chirurgie. Met het toenemen van de ervaring zou de ideale leeftijd van de chirurgie echter kunnen dalen.
- Het vergroten van de ervaring op het gebied van de chirurgische behandeling van patiënten met een cloacale malformatie is een essentieel onderdeel van het verbeteren van de uitkomsten in deze patiënten. Dit zou bereikt kunnen worden door het creëren van Expertisecentra op het gebied van deze aandoening en door middel van internationale samenwerkingsverbanden die zich op dit soort aandoeningen focussen, zoals het ARM-net.

- De multidisciplinaire follow-up van patiënten met cloacale malformaties is essentieel in het adequaat vaststellen en behandelen van problemen, deze follow-up zou ten minste moeten bestaan uit chirurgische, urologische, gynaecologische en psychologische en psychosociale begeleiding (Tabel 8.2)
- Indien de follow-up van patiënten met een cloacale malformatie wordt uitgebreid, dienen de zorgdragende expertisecentra ook hun verantwoordelijkheid te nemen inzake de transitie van deze patiënten van de zorg door de kinderspecialismen naar de volwassenen equivalent (chirurg, uroloog, etc.) De ideale transitie lijkt te bestaan uit de betrokkenheid van zowel de kinderspecialist en een betrokken volwassenenspecialist, resulterend in een samenwerking tussen beiden waarin laagdrempelig contact en overleg mogelijk is.

Appendices

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List of publications

PhD portfolio

Curriculum vitae

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List of publications

Versteegh HP, Adams S, Boxall S, Burge D, Stanton MP. Antenatally diagnosed right sided stomach (Dextrogastria) – 10 year experience. J Pediatr Surg 2015; accepted for publication

Ashton JJ, **Versteegh HP**, Batra A, Afzal NA, King A, Griffiths DM, Beattie RM, Stanton MP. Colectomy in paediatric Ulcerative Colitis; a single centre experience of indications, outcomes and complications. J Pediatr Surg 2015; accepted for publication

Versteegh HP, van den Hondel D, IJsselstijn H, Wijnen RMH, Sloots CEJ, de Blaauw I. Cloacal malformation patients report similar quality of life as female patients with less complex anorectal malformations. J Pediatr Surg 2015; accepted for publication

Hofmeester MJ, Draaisma JMT, **Versteegh HP**, Huibregtse ECP, van Rooij IALM, de Blaauw I. Perioperative nutritional management in congenital perineal and vestibular fistulas: A Systematic Review. Eur J Pediatr Surg 2015; accepted for publication.

Versteegh HP, Sutcliffe JR, Sloots CEJ, Wijnen RMH, de Blaauw I. Postoperative complications after reconstructive surgery for cloacal malformations: a systematic review. Techn Coloproctol 2015; 19: 201-207.

Versteegh HP, Wolffenbuttel KP, Sloots CEJ, Madern GC, van den Hoek J, Wijnen RMH, de Blaauw I. Effects of reconstructive surgery on bladder function in patients with anorectal malformations. J Urol 2014; 192: 1789-1793.

Versteegh HP, Sloots CEJ, Wolfenbuttel KP, de Jong JR, Sleeboom Chr, Feitz WF, van Heurn LWE, van der Zee DC, Wijnen RMH, de Blaauw I. Urogenital function after cloacal reconstruction, two techniques evaluated. J Pediatr Urol 2014; 10: 1160-1164.

Versteegh HP, Sloots CEJ, de Jong JR, Sleeboom Chr, Rassouli R, van Heurn LWE, van der Zee DC, Wijnen RMH, de Blaauw I. Early versus late reconstruction of cloacal malformations; the effects on postoperative complications and long-term colorectal outcome. J Pediatr Surg 2014; 49: 556-559.

Versteegh HP, van Rooij IALM, Levitt MA, Sloots CEJ, Wijnen RHM, de Blaauw I. Long-term follow-up of functional outcome in patients with a cloacal malformation: a systematic review. J Pediatr Surg 2013; 48: 2343-2350.

Versteegh HP, Feitz WFJ, van Lindert EJ, Marcelis C, de Blaauw I. "This bicycle gives me a headache", a congenital anomaly. BMC Res Notes 2013; 6: 412.

De Blaauw I, Midrio P, Breech L, Bischoff A, Dickie B, **Versteegh HP**, Peña A, Levitt MA. Treatment of Adults with Unrecognized or Inadequately repaired Anorectal Malformations: 17 Cases of Rectovestibular and Rectoperineal Fistulas. J Pediatr Adolesc Gynecol 2013; 26: 156-160.

Versteegh HP, Bakia A, Koopman HM, Kraaij V, Versteegh FGA. Evaluation of HIV and AIDS knowledge in rural Cameroon men with use of a questionnaire. Pan Afr Med J 2013; 16: 141.

PhD portfolio

Erasmus MC
Universitair Medisch Centrum Rotterdam

Summary of PhD training and teaching

Name PhD student:	Hendt Paul Versteegh	PhD period:	June 2011 – November 2015
Erasmus MC department:	Pediatric Surgery	Promotor:	Prof. Dr. R.M.H. Wijnen
	Sophia Children's Hospital Erasmus Medical Center	Supervisors:	Dr. I. de Blaauw Dr. C.E.J. Sloots

1. PhD training		Year	Workload
General courses			
BROK course, Erasmus MC	Erasmus Medical Center	2013	1 ECTS
CPO mini course (patient orientated research and preparation for subsidy application)	Erasmus Medical Center	2013	0.3 ECTS
Research integrity, dept. medical ethics and philosophy, Erasmus MC	Erasmus Medical Center	2013	2 ECTS
Specific courses and workshops			
4th Annual Pedatric Colorectal Workshop	Sophia Children's Hospital	2011	1 ECTS
5th Annual Pedatric Colorectal Workshop	Sophia Children's Hospital	2012	1 ECTS
6th Annual Pediatric Colorectal Workshop	Sophia Children's Hospital	2013	1 ECTS
7th European Pediatric Colorectal Symposium	Hannover, Germany	2014	1 ECTS
Presentations			
19th International Meeting of the Pediatric Colorectal Club (Oral) *Functional outcome in patients with a cloacal malformation; the Dutch experience 1985-2009*	Rome, Italy	2012	1 ECTS
13th Congress of the European Paediatric Surgeons' Association (Oral) *Complications and anorectal function in patients with a cloacal malformation.*	Rome, Italy	2012	1 ECTS
13th Congress of the European Paediatric Surgeons' Association (Poster) *Urological outcome in patients with a cloacal malformation.*	Rome, Italy	2012	0 ECTS
20th International Meeting of the Pediatric Colorectal Club (Oral) *Long-term follow-up of functional outcome in patients with a cloacal malformation: a systematic review.*	Frankfurt, Germany	2013	1 ECTS

15th Congress of European Paediatric Surgeons' Association (Oral (1)) *Postoperative complications after reconstructive surgery for cloacal malformations: our series and a systematic review of literature.*	Dublin, Ireland	2014	1 ECTS
15th Congress of European Paediatric Surgeons' Association (Oral (2)) *Effects of reconstructive surgery on urodynamics in patients with anorectal malformations.*	Dublin, Ireland	2014	1 ECTS
(Inter)national conferences			
19th International Meeting of the Pediatric Colorectal Club	Rome, Italy	2012	1 ECTS
13th Congress of the European Paediatric Surgeons' Association	Rome, Italy	2012	1 ECTS
6th Rotterdam Interactive Congress on Hernia	Rotterdam, the Netherlands	2012	0.3 ECTS
20th International Meeting of the Pediatric Colorectal Club	Frankfurt, Germany	2013	1 ECTS
15th Congress of European Paediatric Surgeons' Association	Dublin, Ireland	2014	1 ECTS
27th Symposium Experimenteel Onderzoek Heelkundige Specialismen	Groningen, the Netherlands	2014	0.4 ECTS
Annual congress of British Association of Paediatric Surgeons	Cardiff, United Kingdom	2015	1 ECTS
Other			
Clinical fellowship (6 weeks) at the department of paediatric surgery, Southampton University Hospital	Southampton, United Kingdom	2014	3 ECTS
Local organizing committee of the 8th Pediatric Colorectal Course and Workshop.	Radboud UMC, Nijmegen, the Netherlands	2015	3 ECTS

2. Teaching

Lecturing

Erasmus Anatomy Research Project (EARP, anatomy masterclass) Limb anatomy	Erasmus Medical Center	2011	3 ECTS
Erasmus Anatomy Research Project (EARP, anatomy masterclass) Thoracic anatomy	Erasmus Medical Center	2012	3 ECTS
Lecture at the Child health grand round at Southampton University Hospital *Cloacal malformations; diagnosis, treatment, and outcome in the Netherlands.*	Southampton, United Kingdom	2014	1 ECTS
Lecturing primary school children on the subject of basic human anatomy and physiology, Calvijn primary school	Rotterdam, the Netherlands	2014	0.4 ECTS
Lecture at the Early Bird teaching sessions at Reinier de Graaf Gasthuis	Delft, the Netherlands	2015	0.1 ECTS

Supervising practicals and excursions, tutoring

Erasmus anatomy and research project (EARP, anatomy masterclass) Thoracic anatomy (tutoring)	Erasmus Medical Center	2013	3 ECTS

Curriculum vitae

Hendt Paul Versteegh was born on May 8th 1987 in Rotterdam. After growing up in Waddinxveen, he attended secondary school (Coornhert Gymnasium) in Gouda, of which he graduated in 2005. The next year, before starting his medical training, he travelled to Cameroon, West-Africa, to work as a volunteer and to give HIV/AIDS education in the Apostolic Hospital, Banga Bakundu, Southwestern province. In 2006 Hendt was able to start his medical training in Rotterdam. In 2009 he once again travelled to Cameroon in good company of Rintje Agricola to spend several weeks at the Holy Family Medical Centre, Akum, Northwestern province (Supervisor: dr. Affuenti Bakia) as part of a third year scientific elective. In 2011 he finished his theoretical medical studies after doing a five months scientific elective at the department of pediatric surgery on the subject of cloacal malformations (supervisor: I. de Blaauw, MD, PhD). After these first five months he got the opportunity to proceed with this research as a PhD candidate at the department of pediatric surgery (head: Prof. R.M.H. Wijnen, MD, PhD). In order to finish his medical school, he started his clinical rotations in August of 2012. The final part of these rotations were spent at the Reinier de Graaf Gasthuis hospital in Delft (department of surgery, supervisor: dr. M. v/d Elst) and at the Southampton General Hospital, Southampton, United Kingdom (department of pediatric surgery, supervisor: M. Stanton). After obtaining his medical degree in September 2014 he returned to the department of pediatric surgery in order to proceed on his PhD research. In January 2015 he started as a resident (SHO/ANIOS) at the department of surgery at the Reinier de Graaf Gasthuis hospital in Delft (supervisor: M. v/d Elst).

Dankwoord

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