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LONG-TERM ACTIVE PROBLEMS IN PATIENTS WITH CLOACAL EXSTROPHY: A SYSTEMATIC REVIEW

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LONG-TERM ACTIVE PROBLEMS IN PATIENTS WITH CLOACAL EXSTROPHY: A SYSTEMATIC REVIEW

Layla Musleh MD [1,2]*, Laura Privitera MD [3,4]*, Irene Paraboschi MD [3,4], Alexios Polymeropoulos PhD [5], Imran Mushtaq MD[6], Stefano Giuliani MD, PhD [1,3,4]

[1] Department of Specialist Neonatal and Paediatric Surgery, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

[2] Pediatric Surgery Unit, San Camillo Forlanini Hospital, Rome, Italy

[3] Wellcome / EPSRC Centre for Interventional and Surgical Sciences (WEISS), London, United Kingdom

[4] Developmental Biology and Cancer Research Department, UCL GOS Institute of Child Health, London, United Kingdom

[5] Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

[6] Department of Paediatric Urology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom.

Institutions information:

Great Ormond Street Hospital for Children NHS Foundation Trust

Department of Specialist Neonatal and Paediatric Surgery

Great Ormond Street, London WC1N 3JH, United Kingdom

www.gosh.nhs.uk

San Camillo Forlanini Hospital

Department of Pediatric Surgery

Circonvallazione Gianicolense, 87, Rome 00152, Italy

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

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http://www.scamilloforlanini.rm.it/

Wellcome / EPSRC Centre for Interventional and Surgical Sciences (WEISS)

University College of London

43 - 45 Foley Street, London W1W 7TS, United Kingdom

www.ucl.ac.uk/interventional-surgical-sciences/

UCL Great Ormond Street Institute of Child Health

Developmental Biology and Cancer Research Department

30 Guilford Street, London WC1N 1EH, United Kingdom

www.ucl.ac.uk

University of Milano-Bicocca

Department of Statistics ad Quantitative Methods

1 Piazza dell'Ateneo Nuovo, Milan 20126, Italy

www.unimib.it

Corresponding author:

Mr Stefano Giuliani FRCS (Eng) MD (Ita) MD (USA) PhD

Consultant Neonatal and Paediatric Surgeon,

Department of Specialist Neonatal and Paediatric Surgery,

Great Ormond Street Hospital for Children, London, United Kingdom

Email: Stefano.Giuliani@gosh.nhs.uk

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'Layla Musleh and Laura Privitera contributed equally to the manuscript'

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HIGHLIGHTS

- **What is currently known about this topic?**
- Cloacal exstrophy is a rare congenital condition that affects multiple organs, including bladder, colon, spine and external genitalia. While data regarding short- and medium-term outcomes are easily accessible in the literature, only a few case reports and heterogenous series discuss late medical problems.
- **What new information is contained in this article?**
- This article reports the prevalence of long-term active medical problems affecting cloacal exstrophy patients after the first decade of life. Our results show that different aspects of these patients' lives are deeply affected in the long-term for urinary continence, sexual function, gender identity, ambulatory capacity and psychological well-being.

STRUCTURED ABSTRACT

Background: Cloacal exstrophy (CE) is the most severe end of the Exstrophy-Epispadias Complex malformations spectrum. Improvements in post-natal management and well-established operative techniques have resulted in survival rates approaching 100%. This systematic review aims to define the prevalence of long-term active medical problems affecting CE patients after the first decade of life.

Methods: PubMed/Medline, Embase, Scopus, and ISI Web of Knowledge databases were used for the literature search. Original articles related to medical, surgical, and psychosocial long-term

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

problems in CE patients >10 years of age were included in the study. Quality assessment of the articles was performed through the Newcastle-Ottawa Scale. Prevalence estimates and 95% CI were assessed for each outcome.

Results: Twelve studies were included. The most common long-term active problems identified were: urinary incontinence with a prevalence ranging from 9.1% to 85%; sexual function issues related to vaginal anomalies with a prevalence ranging from 8.3% to 71.3%, and uterine anomalies, with a prevalence from 14.3% to 71%; gender identity issues in 46, XY patients raised female had a prevalence from 11.1% to 66.7%. There is no documented history of paternity. Impairment of ambulatory capacity was recorded in 13.8% of patients. Only one paper studied psychological well-being, reporting significantly higher levels of depression among gender reassigned patients.

Conclusions: Teenagers and adults born with CE have well defined long-term problems compared to the general population. Recognition and expert management are crucial to improve care and quality of life during and after the transition into adulthood.

KEYWORDS: Cloaca Exstrophy; Long-term outcomes; Urinary Outcomes; Gastrointestinal outcomes; Gender identity issues.

LEVEL OF EVIDENCE Level I.

ABBREVIATIONS:

CE = Cloaca Exstrophy

QoL = Quality of Life

CKD = Chronic Kidney Disease

eGFR = estimated Glomerular Filtration Rate

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

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CIs = Confidence Intervals

HIGHLIGHTS

What is currently known about this topic?

Cloacal exstrophy is a rare congenital condition that affects multiple organs, including the bladder, colon, spine and external genitalia. While data regarding short- and medium-term outcomes are easily accessible in the literature, only a few case reports and heterogenous series discuss late medical problems.

What new information is contained in this article?

This article reports the prevalence of long-term active medical problems affecting cloacal exstrophy patients after the first decade of life. Our results show that these are the most common active problems after puberty in patients born with CE:: urinary continence, sexual function, gender identity, ambulatory capacity and psychological well-being.

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INTRODUCTION

Cloacal Exstrophy (CE) is the rarest disorder among the Bladder Exstrophy-Epispadias-Cloacal Exstrophy Complex (BEECEC) with an estimated incidence of 1:200.000 to 1:400.000 live births [1,2]. Clinical features comprise the exstrophy of two hemibladders, separated in the midline by a caecal plate. It is typically associated with exomphalos, imperforate anus and genital schisis. While the terminal ileum usually prolapses through the exposed cecum, the colon distal to the cecal plate is variably foreshortened [3,4]. The frequent association of CE with urogenital, gastrointestinal, skeletal and neurological malformations defines the Omphalocele, Exstrophy, Imperforate anus and Spinal defect (OEIS) complex, with a reported prevalence of 1:82.000 to 1:200.000 life births [5].

CE complexity and related anatomical defects play a pivotal role in urinary, gastrointestinal, gynaecological and neurological long-term outcomes, potentially affecting patients' overall quality of life (QoL). Whilst data on the short- and medium-term outcomes is available in the literature, only a few case reports and heterogenous series refer to the long-term active medical problems affecting patients with CE beyond the first decade of life [2–4,6].

It is crucial to identify the most significant medical issues children with CE will face as young adults. This systematic review aims to define the prevalence of long-term active medical problems affecting CE patients after the first decade of life. Early recognition and effective management of these complex problems will lead to improved outcomes and facilitate an effective and more focused transition to a better prepared adult multidisciplinary team.

MATERIAL AND METHODS

Search Strategy

No ethics committee or institutional review board approval was required. PubMed/Medline,

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

Embase, Scopus, and ISI Web of Knowledge databases were accessed to perform the literature search in September 2020 (Table 1). All the papers reporting clinical outcomes in full-length articles published in English, Italian or French between 1960 and September 2020 were selected. Literature search was completed by examination of article references for any missed relevant study. The reference lists of all systematic reviews in the field were also screened for additional references.

Inclusion Criteria

We included original articles related to medical, surgical and psychosocial long-term problems reported in patients above 10 years of age with CE. In those papers, which included a diverse age-population of patients born with congenital malformations, data were extracted selectively for the subgroup of patients who met the inclusion criteria.

Exclusion Criteria

We excluded patients with less than ten years of age to provide a reasonable timespan to assess long-term clinical and surgical outcomes. Non-English, non-French, non-Italian language papers were excluded. Review articles, conference abstracts, case reports and articles with less than five patients were excluded because prevalence estimates obtained were considered unreliable. Papers describing solely surgical techniques were also excluded.

Data Extraction

After the removal of duplicates, the search was performed by two independent reviewers (L.M. and L.P.). The first selection was made based on the papers' title to remove irrelevant reports, while final identification of the included studies was assessed by applying eligibility criteria to abstracts and full texts. Conflicts in screening and selection were solved by a third author (S.G.). Adequate records of the search's results and the application of eligibility criteria were kept in order to

complete a detailed PRISMA flowchart (Figure 1). Full articles were evaluated, and data extracted for additional analysis. Data related to outcomes and characteristics of the study were collected in a spreadsheet file (Microsoft Excel®). Number of patients, age, and management details were extracted from each study. Three independent reviewers were involved (L.M., L.P., I.P.) to limit errors and bias. Information regarding the same patients, presented in different studies, were incorporated and presented once. Selected articles and outcomes were reviewed by a pediatric urology consultant (I.M.), given his experience treating a large volume of patients affected by CE.

Statistical Analysis

For each outcome, prevalence estimates of individual studies were based on Odds and 95% Confidence Intervals (CIs) computed on their original scale. For each associated outcome and study with moderate cases, CIs were based on the logit approximation, whereas for studies with cases=0 or cases=total, 95% CIs were computed by the adjusted Agresti-Coull method. The prevalence estimates and 95% CIs direct computation on their main scale were carried out using the R package ("DescTools"), whereas for the forest plots, the R package ("Metafor") was used. We did not proceed with a metanalysis due to the small number of studies and participants in each survey, as calculations may lead to pooled estimates of inconsistent and unreliable results. Statistical analysis and forest plots were undertaken by a professional statistician (A.P.).

Quality Assessment

Quality assessment was conducted accordingly to the Newcastle-Ottawa Scale. The score was measured using a standardized star allocation system for selection, comparability, and outcome. A maximum score of 9 was given, with scores of <5 considered low, 5-6 medium, and 7-9 high quality (Table 2).

RESULTS

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

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The literature search identified 1534 results. After the screening process, only 12 retrospective studies, published between 1988 and 2017, met the inclusion criteria [7–18]. The total number of CE patients included in this review was 191. The patients' age was reported in 11 articles (91.7%), ranging from 10 to 34 years at the last follow-up.

Among the ten unicentric studies, seven were written by American authors, two by European and one by Asian authors. The remaining two multicentric reports were based on collaboration between either Canadian or Japanese centres and the USA. Eight studies were classified as high-quality [7,9–13,16,17], and four were considered as low-quality [8,14,15,18]. Two out of 12 studies (16.7%) reported outcomes about a clinical variant in 13 patients, termed covered CE [13,14]. In this last condition, intra-abdominal anatomic findings are similar to those described in the classic CE, although the abdominal wall is intact [19]. We included these studies in the review as the bladder and colonic need for reconstruction is similar to that required in CE patients.

Urinary Tract

Six articles discussed long-term urinary system outcomes for a total of 121 patients [8–11,17,18]. Continence status was assessed in 32 patients, with a prevalence of incontinence ranging from 9.1% to 85%. The definition of urinary continence varied among the included articles, described in most of them as dry intervals between catheterization, while Mukherjee et al. labelled incontinent patients as those unable to have spontaneous voiding [11]. Overall, half of the patients were incontinent of urine in the long term. Continence intervals were detailed only for two patients, with one of them voiding spontaneously every 4-6 hours, being dry overnight, and the second patient with clean intermittent self-catheterization every 3 hours. The second patient was also reported to be occasionally wet overnight. Stress incontinence was described for one patient (Figure 2-A). Surgical records were available for 23 out of the 32 patients (Table 3) [8,9,11,18].

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

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Three articles documented the upper urinary tract status in a total of 95 patients. An abnormality of the upper urinary tract was found in 39/95 cases (41.1%), with prevalence ranging from 14.3% to 48% for the largest study (95%CIs, 37.0%- 59.2%) [8,10,17]. Abnormalities included solitary kidney in 27 cases (69.2%), ectopic kidney in 12 cases (30.8%), malrotation of the kidney in 10 cases (25.6%), duplicated collecting system in 2 cases (5.1%), ureteral stenosis in 2 cases (5.1%), uretero-vesical junction obstruction and a congenital cyst in one patient (2.6%), respectively. A specific surgical repair procedure was described only for two patients: a uretero-ureterostomy for a duplicated collecting system and a trans-uretero-ureterostomy for a uretero-vesical junction obstruction (Figure 2-B).

The development of lower urinary complications was described in 3 articles for a total population of 31 patients (Figure 2-C) [9,10,18]. Seven patients (22.6%) developed stones and, the operative management was described for 4 of them. The five patients (16.1%) who previously underwent augmentation and/or urinary diversion reported having occasional or frequent infections. Additionally, three patients (9.7%) developed a hematuria-dysuria syndrome after a gastrocystoplasty.

Renal function was evaluated in 2 articles for a total of 20 patients with a prevalence of chronic kidney disease (CKD) of 15% for one study (95% CIs, 0.0% - 34.5%) and 87.1% for the other (95% CIs, 70.0% - 100.0%) [11,18]. The prevalence of CKD of at least stage 1 was 55% (n=11/20). We could not further analyze the authors' results for the first article as they only reported the available medical characteristics [11]. In the paper by Suson et al., kidney function was assessed pre and post composite bladder augmentation. After the bladder augmentation, only one patient progressed from CKD1 (eGFR >90 ml/min) to CKD2 (eGFR of 60-89 ml/min), while another improved CKD2 to CKD1. In the remaining nine cases, patients had eGFR of >90 ml/min pre-operatively and

postoperatively. None of them progressed to end-stage renal disease [18].

Gastrointestinal tract

Only one article investigated faecal incontinence of 8 patients, of which: 3 (37.5%) had a stoma formation at seven days of life (two ileostomies and one colostomy), and 5 (62.5%) underwent a colonic pull-through. Only one patient who underwent colonic pull-through was described as faecal continent using appropriate bowel management (enemas and anticholinergic medications) [7]. From a surgical point of view, in one case (3.6%), a pull-through failure was corrected through a Hartman's pouch and colostomy formation that subsequently required conversion to a terminal ileostomy because of recurrent prolapse. In 3 cases (10.7%), a stoma revision was needed later on. In terms of post-operative complications, four patients had a bowel obstruction, two patients had a stoma prolapse, and one patient developed an enteric fistula [7].

In the long term, five patients (16.1%) developed episodic hyponatremia and metabolic disorders [7,18]. In general, the frequency of hospitalization due to electrolyte imbalances and dehydration becomes rare after 3 years of age; however, the remaining cases developed occasional dehydration episodes during coexisting viral gastroenteritis [7]. One patient developed mild metabolic alkalosis following composite bladder augmentation construction [18]. Among the papers selected, one case of a 15 years old girl showed mild short bowel syndrome and one case of a 27-year-old patient who showed a bodyweight of less than 5% compared to growth nomogram [7,8].

Reproductive System

Female population

Four articles analyzed long-term outcomes of the reproductive system with a total of 56 female patients [9,13,14,16]. Vaginal anomalies showed a prevalence ranging from 8.3% (95% CIs, 1.2% - 41.3%) to 71.3% (95% CIs, 53% - 84.1%) (Figure 3-A). Thirty-two out of 56 patients presented

vaginal-related issues, and the anomalies described include vaginal duplication in 20 cases (62.5%), vaginal hypoplasia in 5 patients (15.6%), vaginal atresia in 4 patients (12.5%), prolapse in 2 patients (6.2%) and vaginal ectopia in 1 case (3,1%). Surgical records regarding vaginal reconstructive surgery was reported for 23 patients including: no-specified vaginoplasty in 8 (34.8%), cystovaginoplasty in 4 (13.4%), intestinal vaginoplasty in 3 (13.0%), colporrhaphy in 3 (13.0%), vaginal septum incision in 2 (8.7%), vaginectomy in 1 patient (4.4%), pull-through vaginoplasty in 1 (4.4%), and sacrocolpopexy in 1 (4.4%). Another study by Suson et al. reported not specified Mullerian anomalies in 23 out of the 35 female patients of their population (65.7%) [17].

The same cohort of patients was also analyzed for uterine problems, showing a prevalence ranging from 14.3% (95% CIs, 2.0% - 58.1%) to 71% (95% CIs, 53.0% - 84.1%) (Figure 3-B). The uterine anomalies described for 21 out of 56 (37.5%) patients were as follow: duplication in 14 (66.7%), uterine atresia in 2 (9.5%), ectopia in 2 (9.5%), not-specified haemato- and hydro-colpos in 2 (9.5%) and uterine prolapse in one (4.8%). The related surgical procedure performed was reported in 14 patients (66.7%). Eight out of 14 patients (57.1%) had a hemi-hysterectomy, and 6/14 had a total hysterectomy (42.9%). None of the articles described any tubal or ovarian problems.

Regarding the sexual activity of CE patients, four studies investigated this with a total of 56 patients (Figure 3-C). The largest study, which included data analysis from 31 patients with an age range of 20-25 years, showed a prevalence of 9.7% (95%CIs, 3.2% - 26.1%) for the number of patients being sexually active. Overall, only 10/56 patients (17,9%) declared themselves to be sexually active. Successful pregnancy was reported in 2/49 women (4.1%), and a miscarriage occurred in 2/49 women (4.1%) (Figure 3-D). A marriage was reported in 2 out of 18 (56%) of women questioned.

Male population

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Although not eligible for the statistical analysis, we decided to include some data about the reproductive outcomes in males, as long-term problems such as phallic inadequacy and its associated psychological sequelae are substantial.

Husmann et al. analyzed the management of four post-pubertal genotypic male patients. In all cases, after completion of a 2-staged urethroplasty, stretched penile lengths were at or below two standard deviations below the mean on standard penile growth nomograms. Serum testosterone determinations were within normal adult male limits (540 - 750 ng/ml). Sexual histories revealed feelings of sexual inadequacy in all patients, with 3 of them requiring intensive psychiatric counselling. The presence of erectile capability was confirmed only for 2 out of 4 patients. One was unable to penetrate the vagina due to phallic inadequacy, and the other was married and engaging in successful vaginal intercourse. The semen analysis revealed azoospermia with retrograde ejaculation in 2 patients, while in the other patient, semen evaluations revealed normal motility and morphologic parameters (counts range: 20 - 40 million). No documented history of paternity exists [20].

In another exploratory study published in 2014, sexual QoL was assessed in 10 men at least one year after phalloplasty. Of them, only one patient of 22 years of age was affected by CE and resulted in severe penile insufficiency. Penile reconstruction was performed using the modified technique of anterolateral thigh flap along with the insertion of a penile prothesis (AMS Ambicor™, 1 cylinder, 16 cm) [21].

Gender Assignment and Behavior Issues

The concept of sex assignment and gender identity is of special importance for clinicians. Concerning gender assignment at birth, out of the 38 genetic male patients, a female gender assignment was reported in 27 patients (71.1%). Patients' year of birth was between 1970 and 1990. In details, the prevalence of female gender assignment at birth among the included studies goes

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from 44.4% (95% CI, 17.7% - 74.9%) to 85.7% for the largest study (95% CI, 57.3% - 96.4%) (Figure 3-E) [10–12,15,18].

Three studies further investigated the prevalence of gender reassignment among these patients, which turned out to be 13 out of 26 cases (38.5%) (Figure 3-F) [10,15,18]. In the study by Reiner et al., six detailed questionnaires evaluating the subjects' psychosexual development and sexual identity (subjects' interests; aggressive behaviours; career interests; sexual interests) showed moderate-to-marked male-typical behaviours in all the subjects despite their gender assignment at birth [10].

Deambulatory Capacity

Impairment in terms of deambulatory capacity can be a result of both spinal and lower limb anomalies. In our selected articles, these elements were analyzed in a cohort of 29 patients [10–12]. Scoliosis was reported in 5/29 patients (17.2%) and tethered cord in 3/29 patients (10.3%). Three (10.3%) patients with tibia–fibula agenesis resulted in a prosthesis insertion, and one patient (3.4%) required a clubfoot repair. Impaired ambulatory capacity was described in 4/29 patients (13,8%), of which two patients used leg braces, and two patients were wheelchair users [10,11]. Also, bone health was analyzed in 6 (20.7%) patients that, regardless of the presence of osteoporosis risk factors, showed good bone mineral density and adjusted z-scores during adolescence [12].

Psychosocial Issues

A single article assessed the psychosocial well-being, gender and cognitive ability of 9 patients based on semi-structured interviews [11]. The authors compared gender assigned patients (N=3) to non-assigned patients with CE (N=6). Depression scores ranged from minimal to mild across the two groups, with assigned patients (33.3%) showing a significantly higher level of depression on the BDI-II and SCL-90-R depression sub-scale (6.87±8.42 vs 15.66±7.02). There were no significant differences regarding anxiety on other sub-scales of the SCL-90R and the BAI. As far as

self-esteem and social adjustment, SAS-SR results showed a not significant poorer social adjustment compared to normative means.

DISCUSSION

CE represents a complex condition involving urological, colorectal, Mullerian, neurological systems, and it can significantly affect lifelong patients' QoL. This review quantifies for the first time the prevalence of long-term active issues related to teenagers and adults born with CE. The most common active problems were urinary incontinence (prevalence range 9.1% - 85%), vaginal anomalies (prevalence range 8.3% - 71.0%), uterine anomalies (prevalence range 14.3% - 71%) and gender identity issues in 46,XY patients raised female (prevalence range 11.1% - 66.7%). We have also identified gaps in knowledge that will require future research, such as male and female fertility, QoL, and psychological well-being.

Comparison With Previous Literature

Urinary incontinence appears to be one of the most long-term active problems in patients with CE. The prevalence of urinary incontinence ranges between 9.1% to 85% and is higher than the one reported in patients born with anorectal malformation (ranging between 1.7% and 30.5%) [22]. A recent systematic review estimated that the adult population younger than 40 years had a pooled prevalence rate of urinary incontinence of 16.5% [23]. Considering younger age groups, a review published in 2000 reported a rate of urinary incontinence in 6% of boys and 4% of girls aged between 10 and 11 years, while 3 to 27% suffered from the same problem later in life (17-29 years) [24].

Faecal incontinence after pull-through reconstruction was reported only in one study, with a prevalence of 87.5% [7]. This result is not surprising considering that most surgeons do not attempt

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a pull-through operation due to the often complete absence of pelvic floor and anal sphincter muscle complex. A population-based study conducted in the Netherlands on encopresis prevalence showed faecal incontinence in 1.6% (11-12 age group), and similar results were discovered in the population of southeast Nigeria (1.6% in the 10-year-old population) [25,26]. A recent metanalysis, studying long-term anorectal malformation outcomes, demonstrated that the prevalence of faecal incontinence was 16.7%, which isisfive times lower than we found in CE patients [22]. Based on these data, we believe that children born with CE should have a permanent colostomy without any attempt of a pull-through.

In addition, CE is a structural disorder of sex development. For decades, gender assignment and surgical reconstruction have been the main challenges in these patients. Historically, male infants with an "inadequate" phallus were routinely assigned to the female gender [27]. However, the management has changed as it was shown that gender development and role behaviour were more related to the impact on the brain by prenatal sex hormones [6,28–30]. Regardless of the gender assignment of 46, XY patients at birth, those infants identified themselves as male and reported significant psychological problems when raised as girls [1,11,15,30–33]. In our review, 27 male patients were assigned to a female sex of rearing at birth. In the study by Reiner et al., although all patients' behaviour and attitudes appeared to reflect strong male-typical characteristics, the ultimate gender identity of the 14 patients who were assigned to be female in the neonatal period was unpredictable [10]. The data on the divergent sexual outcomes of these subjects highlight the need for more research and a careful evaluation by an expert multidisciplinary team.

Limited data is now available regarding sexual and reproductive function in young CE adults with a non-reconstructed penis [20-21]. However, given the recent trend of not assigning a female gender to male genetic patients, it is essential to study and report functional outcomes associated with new phalloplasty techniques in this group of patients. We also did not find any documented history of

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paternity. Although intracytoplasmic sperm injection has been successfully performed in other forms of the BEECEC, no history of spontaneous or medically assisted fatherhood in CE patients was ever reported [34]. Thus, healthcare practitioners should be prepared to counsel for assisted reproductive technology, existing the possibility of not achieving spontaneous fatherhood in CE patients [20].

Optimizing pregnancy outcomes requires awareness of the reconstructed abdominopelvic anatomy that should be protected while planning a cesarean delivery. In a previous literature review, Vilanova-Sanchez et al. analyzed the obstetrical outcomes in patients with anorectal malformations, including persistent cloacal anomalies. Their results showed that 7 out of 26 pregnancies (27.0%) had an unsuccessful outcome because of miscarriage in 5 cases and ectopic pregnancy in 2 cases [34]. Both these results are higher than the rate of spontaneous abortion rate reported in the general population being around 14.0% [35]. Since 17.8% of CE female patients declared themselves sexually active (in presence of regular periods), they bear the possibility to carry on pregnancies. As a focus of the transition care, conception, contraception, and delivery may require a multi-specialist team made of geneticists, gynaecologists/urologists, infertility specialists, obstetricians. Thus, surgical management of these women should be discussed with expert paediatric urologists considering their complex reconstructed anatomy [36].

Our review reported an overall rate of 13.8% of ambulatory impairment, mainly due to the long-term sequelae of spinal defects and lower limb abnormalities. Spinal cord surgery, often performed during the first year of life, is essential to enhance lower limb mobility and preserve optimal neurological function. Nevertheless, considering the possibility of spinal cord tethering with subsequent loss of gradual neurological function over time, a need for lifelong awareness is needed to preserve mobility, independence and overall well-being of these individuals[37].

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To conclude, only one eligible article objectively analyzed the psychological well-being during the transition period into adulthood. The results of this study revealed a minimal-mild depression among the CE patients, with higher levels of depression in those males who underwent a female gender assignment at birth. Three other studies, not included in our systematic review due to the small cohort size, are discussed here for completeness. In the already mentioned study by Husmann et al., feelings of sexual inadequacy were found in all post-pubertal patients [20]. In 2002, Zderic et al. reported on the psychological outcomes of three adult male patients assigned female at birth. One patient reported chronic depression, requiring extensive psychiatric support for suicidal ideations [38]. In 2006, Mouriquand et al. assessed the QoL of 23 female patients over 18 years of age with the only CE case of this cohort, complaining of severe urinary incontinence and having severe symptoms of "mental breakdown" [39]. In this regard, we believe it is sensible to advocate early and long-term psychologic support with specialized counselling to help patients and families coping with multiple hospitalizations and abnormal external genitalia.

The implication for Future Research

CE is a rare but highly debilitating condition in the long term. Prenatal diagnosis and the possibility of termination of pregnancy has led to a reduction in the number of CE patients. Multicentric studies are needed to collect robust prospective data and develop evidence-based management protocols to equalize different practices in all aspects of the complex care of these patients. However, given the reduced number of cases and the complex post-natal and long-term complications, we believe that centralization of care for CE would help as much as the one we have for bladder exstrophy in the United Kingdom [40]. In order to achieve an effective transition to adult health care, data should be recorded in an organized database, including data on psychological issues and male sexual and genital outcomes after puberty (often under-represented). Lastly, we also need a consensus on the most effective neonatal reconstructive techniques to achieve the best potential in childhood and adulthood. In order to achieve this, we want to emphasize the need for

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early and life-long multidisciplinary management, which should bring together the expertise and skills of different professionals, including pediatric orthopaedic, general and urology surgeons, gynaecologists, psychologists, and sex therapists. This is essential to provide the best possible and complete treatment for these children and young adults.

Strength and Limitations

This is the first systematic review that reports the current frame about long-term clinical outcomes in patients affected by CE after the first decade of life. The main limitation is represented by the small number of articles and the overall cohort of patients. For this reason, it was not possible to stratify results according to different subgroups. Also, as the articles were considerably heterogeneous, we decided not to perform a meta-analysis of the results as this would have led to incorrect conclusions.

CONCLUSION

Teenagers and young adults born with CE suffer from several active long-term problems compared to the general population. A well-coordinated transition of care and more research in the field are essential elements for improving long-term outcomes and quality of life

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'Layla Musleh and Laura Privitera contributed equally to the manuscript'

Fig. 1. Algorithm for study selection modified from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart**.**

Fig. 2. Forest plots of the reported prevalence for patients with cloacal exstrophy regarding (A) urinary incontinence, (B) anomaly of the upper urinary tract and (C) lower urinary complications.

Fig. 3. Forest plots of the reported prevalence for patients with CE regarding (A) vaginal anomalies, (B) uterine anomalies, (C) sexual activity, (D) pregnancies, (E) female assignment at birth and (F) gender reassignment.

Table 1. Search Strategies performed in September 2020 through the main biomedical literature databases.

Database	Search Strategies
Pubmed	("Cloaca/abnormalities"[Mesh]) OR ("extrophy of the cloaca" OR "cloaca extrophy" OR "cloacal extrophy")
Embase	cloaca/ and exp congenital malformation and (cloaca* adj5 extroph*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
Web of Science	cloaca* NEAR/4 exstroph*
Scopus	cloaca* W/4 exstroph*

Table 2. Demographics and quality scoring of included studies for meta-analysis.* MR Multicentric Retrospective. UR Unicentric Retrospective. †Quality score as per stars awarded by Newcastle–Ottawa Scale for non-randomized trials included in systematic reviews. S: Selection; C: Comparability; O: Outcome. Maximum stars for each study criteria are 4 for selection, 2 for

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comparability, possible score of 9. Higher values indicate a higher-quality study.

Authors	Country	Year of publication	Type of study	Mean age (years)	Age range (years)	Patients Included	Quality score			
							S	C	O	Total
Husmann, DA et al. [7]	USA-Canada	1988	MR	22,5	10-28	8	3	2	3	8
Mitchell, ME et al. [8]	USA	1990	UR	15	10,5-21	6	2	0	1	3
Mathews, RI et al. [9]	USA	2003	UR	ND	>13	6	3	1	4	8
Reiner, WG et al. [10]	USA	2004	UR	13,5	10-21	14	3	2	4	9
Mukherjee, B et al. [11]	USA	2007	UR	ND	11-37	9	3	2	4	9
Taskinen, S et al. [12]	Finland	2008	UR	16	11,5-21	6	3	2	3	8
Naiditch, JA et al. [13]	USA	2013	UR	27,5	10-34	12	3	2	4	9
Hisamatsu, E et al. [14]	Japan	2014	UR	18	11-26	7	2	0	1	3
Vliet, R et al. [15]	Netherlands	2014	UR	23	15-39	6	2	0	1	3
Suson, KD et al. [16]	USA	2016	UR	ND	20-25	31	3	2	3	8
Suson, KD et al. [17]	USA	2016	UR	ND	17-20	75	3	2	3	8
Casey, JT et al. [18]	USA-Japan	2017	MR	24	16-33	11	2	0	1	3

Table 3. Reported urinary reconstructive surgery described for 23 out of 32 patients with a urinary continence status assessed.

Surgical Procedures	***Number (N = 23)***	***%***
BLADDER AUGMENTATION:		
Gastrocystoplasty	14	60.9%
Not-specified bladder augmentation	6	26.0%
Cystectomy with ileal loop urinary diversion	2	8.7%
Ileocystoplasty	1	4.4%
CONTINENT RECONSTRUCTION:		
Monti	7	30.4%
Neo-urethra procedure	5	21.7%
Not specified	5	21.7%
Implantation of an artificial sphincter	2	8.7%
Cystectomies without reconstruction	2	8.7%
Incontinent urinary diversion	1	4.4%

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Appendico-vesicostomy	1	4.4%

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Author contributions:

Layla Musleh and Laura Privitera: contributed to the study conception and design; study selection; quality assessment; data extraction, analysis and interpretation; writing or revising the manuscript for important intellectual content; approval of the final manuscript; equally contributing as principal authors.

Irene Paraboschi: contributed to the study conception and design; quality assessment; data extraction, analysis and interpretation; critical revision of the manuscript; approval of the final manuscript.

Alexios Polymeropoulos: contributed to the acquisition, analysis and interpretation of data for the study; drafting and revising for statistic contents; approval of the final manuscript.

Imran Mushtaq: contributed to the study conception and design; writing and revising the manuscript for important statistic content; approval of the final manuscript.

Stefano Giuliani: contributed to the study conception and design; study selection; data acquisition, analysis and interpretation; writing or revising the manuscript for important intellectual content; approval of the final manuscript; acting as a guarantor of the manuscript.

All the authors agreed to be accountable for all aspects of the manuscript in ensuring that questions related to the accuracy or integrity of any part of it have been appropriately investigated and resolved.

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‘Layla Musleh and Laura Privitera contributed equally to the manuscript’

REFERENCES

[1] Woo LL, Thomas JC, Brock JW. Cloacal exstrophy: A comprehensive review of an uncommon problem. *J Pediatr Urol*. 2010;6(2):102-111. doi:10.1016/j.jpurol.2009.09.011

[2] Phillips TM. Spectrum of cloacal exstrophy. *Semin Pediatr Surg*. 2011;20(2):113-118. doi:10.1053/j.sempedsurg.2010.12.007

[3] Lund DP, Hendren WH. Cloacal exstrophy: A 25-year experience with 50 cases. *J Pediatr Surg*. 2001;36(1):68-75. doi:10.1053/jpsu.2001.20009

[4] Sawaya D, Goldstein S, Seetharamaiah R, et al. Gastrointestinal ramifications of the cloacal exstrophy complex: a 44-year experience. *J Pediatr Surg*. 2010;45(1):171-176. doi:10.1016/j.jpedsurg.2009.10.030

[5] Carey JC, Greenbaum B, Hall BD. The OEIS complex (omphalocele, exstrophy, imperforate anus, spinal defects). *Birth Defects Orig Artic Ser*. 1978;14(6B):253-263.

[6] Schober JM, Carmichael PA, Hines M, et al. The ultimate challenge of cloacal exstrophy. *J Urol*. 2002;167(1):300-304.

[7] Husmann DA, McLorie GA, Churchill BM, et al. Management of the hindgut in cloacal exstrophy: Terminal ileostomy versus colostomy. *J Pediatr Surg*. 1988;23(12):1107-1113. doi:10.1016/S0022-3468(88)80324-5

[8] Mitchell ME, Brito CG, Rink RC. Cloacal Exstrophy Reconstruction for Urinary Continence. *J Urol*. 1990;144(2 Part 2):554-558. doi:10.1016/S0022-5347(17)39521-6

[9] Mathews RI, Gan M, Gearhart JP. Urogynaecological and obstetric issues in women with the exstrophy-epispadias complex: UROGYNAECOLOGY IN THE EXSTROPHY-EPISPADIAS COMPLEX. *BJU Int*. 2003;91(9):845-849. doi:10.1046/j.1464-410X.2003.04244.x

[10] Reiner WG, Gearhart JP. Discordant Sexual Identity in Some Genetic Males with Cloacal Exstrophy Assigned to Female Sex at Birth. *N Engl J Med*. 2004;350(4):333-341. doi:10.1056/NEJMoa022236

[11] Mukherjee B, McCauley E, Hanford RB, et al. Psychopathology, Psychosocial, Gender and Cognitive Outcomes in Patients With Cloacal Exstrophy. *J Urol*. 2007;178(2):630-635. doi:10.1016/j.juro.2007.03.144

[12] Taskinen S, Rintala R, Mäkitie O. Bone health in patients with cloacal exstrophy and persistent cloaca after bladder augmentation. *J Pediatr Surg*. 2008;43(4):700-704. doi:10.1016/j.jpedsurg.2007.12.062

[13] Naiditch JA, Radhakrishnan J, Chin AC, et al. Fate of the uterus in 46XX cloacal exstrophy patients. *J Pediatr Surg*. 2013;48(10):2043-2046. doi:10.1016/j.jpedsurg.2013.02.040

[14] Hisamatsu E, Nakagawa Y, Sugita Y. Vaginal Reconstruction in Female Cloacal Exstrophy Patients. *Urology*. 2014;84(3):681-684. doi:10.1016/j.urology.2014.05.042

[15] Vliet R, Roelofs L, Rassouli-Kirchmeier R, et al. Clinical Outcome of Cloacal Exstrophy, Current Status, and a Change in Surgical Management. *Eur J Pediatr Surg*. 2014;25(01):87-93. doi:10.1055/s-0034-1387943

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

Journal Pre-proof

[16] Suson KD, Preece J, Di Carlo HN, et al. Complexities of Müllerian Anatomy in 46XX Cloacal Exstrophy Patients. *J Pediatr Adolesc Gynecol*. 2016;29(5):424-428. doi:10.1016/j.jpag.2016.01.124

[17] Suson KD, Inouye B, Carl A, et al. Congenital renal anomalies in cloacal exstrophy: Is there a difference? *J Pediatr Urol*. 2016;12(4):207.e1-207.e5. doi:10.1016/j.jpurol.2016.04.008

[18] Casey JT, Chan KH, Hasegawa Y, et al. Long-term follow-up of composite bladder augmentation incorporating stomach in a multi-institutional cohort of patients with cloacal exstrophy. *J Pediatr Urol*. 2017;13(1):43.e1-43.e6. doi:10.1016/j.jpurol.2016.09.013

[19] Bischoff A, Levitt MA, Breech L, et al. Covered cloacal exstrophy – a poorly recognized condition: Hints for a correct diagnosis. *J Pediatr Surg*. 2013;48(12):2389-2392. doi:10.1016/j.jpedsurg.2013.08.011

[20] Husmann DA, McLorie GA, Churchill BM. Phallic reconstruction in cloacal exstrophy. *J Urol*. 1989;142(2 Pt 2):563-564; discussion 572. doi:10.1016/s0022-5347(17)38816-x

[21] Callens N, De Cuypere G, T'Sjoen G, et al. Sexual quality of life after total phalloplasty in men with penile deficiency: an exploratory study. *World J Urol*. 2015;33(1):137-143. doi:10.1007/s00345-014-1283-8

[22] Rigueros Springford L, Connor MJ, Jones K, et al. Prevalence of Active Long-term Problems in Patients With Anorectal Malformations: A Systematic Review. *Dis Colon Rectum*. 2016;59(6):570-580. doi:10.1097/DCR.0000000000000576

[23] Chiarelli P, Bower W, Wilson A, et al.Estimating the prevalence of urinary and faecal incontinence in Australia: systematic review. *Australas J Ageing*. 2005;24(1):19-27. doi:10.1111/j.1741-6612.2005.00063.x

[24] Hunskaar S, Arnold EP, Burgio K, et al. Epidemiology and Natural History of Urinary Incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. 2000;11(5):301-319. doi:10.1007/s001920070021

[25] Van der Wal MF, Benninga MA, Hirasing RA. The Prevalence of Encopresis in a Multicultural Population: *J Pediatr Gastroenterol Nutr*. 2005;40(3):345-348. doi:10.1097/01.MPG.0000149964.77418.27

[26] Roberts RE, Roberts CR, Chan W. One-year incidence of psychiatric disorders and associated risk factors among adolescents in the community. *J Child Psychol Psychiatry*. 2009;50(4):405-415. doi:10.1111/j.1469-7610.2008.01969.x

[27] Tank ES, Lindenauer SM. Principles of management of exstrophy of the cloaca. *Am J Surg*. 1970;119(1):95-98. doi:10.1016/0002-9610(70)90018-8

[28] Ebert A, Scheuering S, Schott G, et al. Psychosocial and psychosexual development in childhood and adolescence within the exstrophy-epispadias complex. *J Urol*. 2005;174(3):1094-1098. doi:10.1097/01.ju.0000169171.97538.ed

[29] Forest MG. Role of Androgens in Fetal and Pubertal Development. *Horm Res*. 1983;18(1-3):69-83. doi:10.1159/000179780

'Layla Musleh and Laura Privitera contributed equally to the manuscript'

Journal Pre-proof

[30] Reiner WG. Psychosexual development in genetic males assigned female: the cloacal exstrophy experience. *Child Adolesc Psychiatr Clin N Am*. 2004;13(3):657-674. doi:10.1016/j.chc.2004.02.009

[31] Reiner WG, Kropp BP. A 7-year experience of genetic males with severe phallic inadequacy assigned female. *J Urol*. 2004;172(6 Part 1):2395-2398. doi:10.1097/01.ju.0000144378.59477.74

[32] Medina LS, Crone K, Kuntz KM. Newborns With Suspected Occult Spinal Dysraphism: A Cost-Effectiveness Analysis of Diagnostic Strategies. *PEDIATRICS*. 2001;108(6):e101-e101. doi:10.1542/peds.108.6.e101

[33] Mathews R, Jeffs RD, Reiner WG, et al. Cloacal exstrophy-improving the quality of life: the johns hopkins experience. *J Urol*. December 1998:2452-2456. doi:10.1097/00005392-199812020-00017

[34] Vilanova-Sanchez A, McCracken K, Halleran DR, et al. Obstetrical Outcomes in Adult Patients Born with Complex Anorectal Malformations and Cloacal Anomalies: A Literature Review. *J Pediatr Adolesc Gynecol*. 2019;32(1):7-14. doi:10.1016/j.jpag.2018.10.002

[35] Gray RH, Wu LY. Subfertility and risk of spontaneous abortion. *Am J Public Health*. 2000;90(9):1452-1454. doi:10.2105/ajph.90.9.1452

[36] El Mhabrech H, Ben Hmida H, Charfi H, et al. Diagnostic anténatal des anomalies de la paroi abdominale antérieure. *Arch Pédiatrie*. 2017;24(10):917-924. doi:10.1016/j.arcped.2017.07.002

[37] McLaughlin KP, Rink RC, Kalsbeck JE, et al. Cloacal exstrophy: the neurological implications. *J Urol*. 1995;154(2 Pt 2):782-784.

[38] Zderic SA, Canning DA, Carr MC, et al. The Chop Experience with Cloacal Exstrophy and Gender Reassignment. In: Zderic SA, Canning DA, Carr MC, Snyder HMcC, eds. *Pediatric Gender Assignment*. Vol 511. Advances in Experimental Medicine and Biology. Boston, MA: Springer US; 2002:135-147. doi:10.1007/978-1-4615-0621-8_9

[39] Catti M, Paccalin C, Rudigoz R-C, et al. Quality of life for adult women born with bladder and cloacal exstrophy: A long-term follow up. *J Pediatr Urol*. 2006;2(1):16-22. doi:10.1016/j.jpurol.2005.07.002

[40] Durkin N, Davenport M. Centralization of Pediatric Surgical Procedures in the United Kingdom. Eur J Pediatr Surg. 2017;27(05):416-421. doi:10.1055/s-0037-1607058

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'Layla Musleh and Laura Privitera contributed equally to the manuscript'