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REVIEW ARTICLE

Treatment guidelines for persistent cloaca, cloacal exstrophy, and Mayer–Rokitansky–Küster–Häuser syndrome for the appropriate transitional care of patients

Masayuki Kubota[1,2] · Yutaka Osuga[1,3] · Kiyoko Kato[1,4] · Kenji Ishikura[1,5] · Kazunari Kaneko[1,6] · Kohhei Akazawa[1,7] · Takeo Yonekura[1,8] · Yuko Tazuke[1,9] · Satoshi Ieiri[1,10] · Akihiko Fujino[1,11] · Shigeru Ueno[1,12] · Yutaro Hayashi[1,13] · Kaoru Yoshino[1,14] · Toshihiro Yanai[1,15] · Jun Iwai[1,16] · Takanori Yamaguchi[1,17] · Shintaro Amae[1,18] · Yuichiro Yamazaki[1,19] · Yoshifumi Sugita[1,20] · Miyuki Kohno[1,21] · Yutaka Kanamori[1,11] · Yuko Bitoh[1,22] · Masato Shinkai[1,23] · Yasuharu Ohno[1,24] · Yoshiaki Kinoshita[1,2]

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Abstract
We developed treatment guidelines (TGs) for appropriate transitional care of the genitourinary system in patients with persistent cloaca (PC), cloacal exstrophy (CE), or Mayer–Rokitansky–Küster–Häuser syndrome (MRKH). These TGs are in accordance with the Medical Information Network Distribution Service (Minds), published in 2014 in Japan. Clinical questions (CQs) concerning treatment outcomes of the genitourinary system, pregnancy and delivery, and quality of life in adulthood were prepared as six themes for PC and CE and five themes for MRKH. We were able to publish statements on chronic renal dysfunction, hydrometrocolpos, and pregnancy, based on four CQs about PC, four about CE, and two about MRKH, respectively. However, due to the paucity of proper manuscripts, we were unable to make conclusions about the correct timing and method of vaginoplasty for patients with PC, CE, and MRKH or the usefulness of early bladder closure for patients with CE. These TGs may help clarify the current treatments for PC, CE, and MRKH in childhood, which have been carried out on an institutional basis. To improve clinical outcomes, systematic clinical trials revealing comprehensive clinical data of the urinary and reproductive systems, especially the length of the common channel in PC, are essential.

Keywords Guideline · Transitional care · Persistent cloaca · Cloacal exstrophy · Mayer–Rokitansky–Küster–Häuser syndrome

Introduction

Persistent cloaca (PC) and cloacal exstrophy (CE) are part of the spectrum of cloacal malformation. PC occurs exclusively in women, whereas CE occurs in both sexes. PC is characterized by confluence of the urethra, vagina, and rectum to the narrow common channel of the cloaca, creating a single opening in the perineum (Fig. 1a). CE is the most severe congenital anomaly of newborns in the field of pediatric surgery, as the lower abdominal wall is not congenitally constructed. Consequently, the intestine of the ileocecal region is eviscerated in a longitudinal direction in the middle of the lower part of the abdomen, and the lateral side of the ileocecal region is occupied by eviscerated right and left hemibladders (Fig. 1b). CE is usually associated with other anomalies, such as omphalocele, divided genital organs, and myelomeningocele or spinal anomalies [1]. In male patients, divided penises are atrophic, and testicles are undescended. Therefore, reconstructive surgery of the genitourinary organs, in addition to anorectoplasty, are necessary for PC and CE.

According to a 2014 nationwide survey of PC and CE in Japan [1], the incidences of PC and CE from 1980 to 2012 were 0.97 and 0.49 per 100,000, respectively; much lower than that of the major congenital anomaly of anorectal malformation (ARM), being 1 per 4000–5000 [2, 3]. The fundamental surgical strategy of anorectoplasty

The present TGs were published in Japanese in book format in March 2017 [20].

✉ Masayuki Kubota
kubotama@med.niigata-u.ac.jp

Extended author information available on the last page of the article

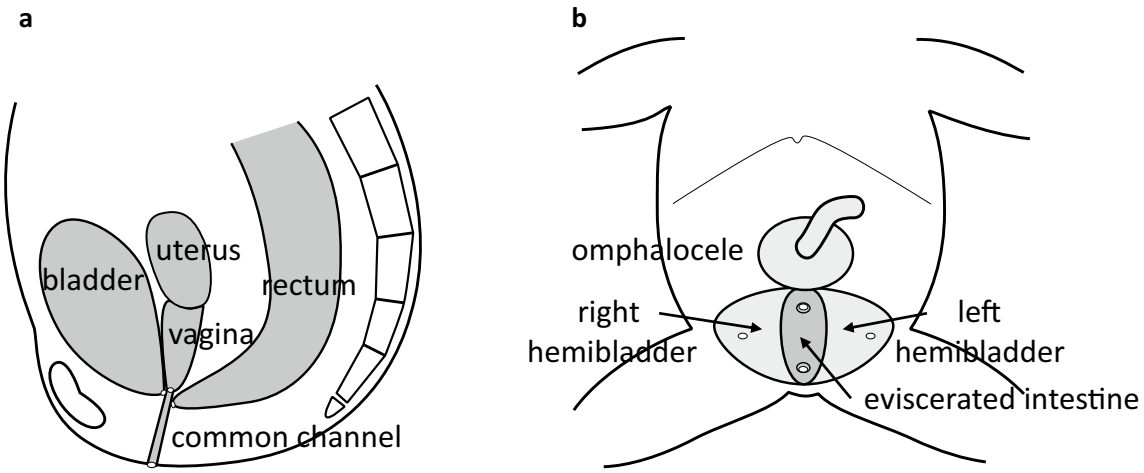

Fig. 1 Schematic illustration of persistent cloaca (PC) and cloacal exstrophy (CE). **a** PC and **b** CE

has improved since the novel technique of posterior sagittal anorectoplasty (PSARP) was introduced by Pena [4]. Laparoscopic-assisted anorectoplasty is also gaining wide acceptance as a new treatment for patients with anorectal malformation [5]. Patients rarely need reoperation for bowel dysmotility or incontinence in adulthood [6]; however, such genitourinary system surgery in pediatric patients is challenging, and surgery performed within a few years after birth continues to result in later clinical problems in adolescents and young adults (AYAs) with PC [7–9] and CE [10–12]. Thus, there is an urgent need to develop appropriate treatment guidelines (TGs) that can facilitate the transitional care of PC and CE patients from childhood to adulthood.

Mayer–Rokitansky–Küster–Häuser syndrome (MRKH) is characterized by Müllerian agenesis with resultant agenesis or atresia of the vagina, uterus, or both, and occurs at an incidence of 1 per 4500–5000 women [13]. MRKH is classified into two types: isolated (type I) and type II (30–40%) with extragenital malformations, such as renal hypoplasia, horseshoe kidney, vertebral anomalies, digital anomalies, or anorectal malformation [14]. Although the diagnosis of MRKH is usually made in puberty during investigations for primary amenorrhea, some cases are detected coincidentally in the neonatal period [15] or early infancy because of associated anomalies or unrelated diseases [16]. The ideal method of vaginoplasty for adults remains a matter of debate [17]; therefore, limited information is available regarding the best method of vaginoplasty for MRKH patients in childhood.

The present TGs summarize the developmental process, available evidence, development of recommendations, and strengths of recommendation for PC, CE, and MRKH. Because the purpose of these TGs is to improve the quality of life (QOL) of patients who undergo genitourinary surgery in childhood, only patients whose MRKH was diagnosed before puberty are included.

TG development process

These TGs were developed according to the procedure released in 2014 by the Medical Information Network Distribution Service (Minds) in Japan [18, 19]. The TG development process included clarifying the purpose of the TGs, organizing a steering committee, organizing a TG committee, setting the scope of the clinical questions (CQs), performing a literature search and systematic review, developing recommendations, writing the first draft of the TGs, performing an external evaluation and obtaining public comments, and releasing the TGs.

(1) *Clarifying the purpose of these TGs*

These TGs for PC, CE, and MRKH were developed to facilitate the transitional care of these patients from infancy to adulthood. Patients who undergo primary treatments as neonates or young infants often need further treatments in the AYA period. The present TGs include evidence-based information, which aids in the early recognition of late problems. It also clarifies the proper timing and methods of these treatments in adults. Such information is vital for improving the QOL of patients, while preserving the residual functions of the compromised genitourinary systems as much as possible. Therefore, the goal of these TGs is to help these patients enjoy a better adult life.

(2) *Organizing a steering committee*

The steering committee comprised six scientists: one pediatric surgeon, two obstetric and gynecologists, two pediatric nephrologists, and one statistic scholar (Table 1).

Table 1 Treatment guideline committee

Steering committee	
Masayuki KUBOTA (chief), Yutaka OSUGA, Kiyoko KATO, Kenji ISHIKURA, Kazunari KANEKO, Kohei AKAZAWA	
TG committee; persistent cloaca	
Takeo YONEKURA (chief), Yuko TAZUKE, Satoshi IEIRI, Akihiro FUJINO, Shigeru UENO, Yutaro HAYASHI, Kaoru YOSHINO	
TG committee; cloacal exstrophy	
Toshihiro YANAI (chief), Jun IWAI, Takanori YAMAGUCHI, Shintaro AMAE, Yuichiro YAMAZAKI, Yoshifumi SUGITA	
TG committee; Mayer–Rokitansky–Küster–Häuser syndrome	
Miyuki KOHNO (chief), Yutaka KANAMORI, Yuko BITOH, Masato SHINKAI, Yasuharu OHNO	
Research collaborators	
Toshiyuki OHYAMA	Department of Pediatric Surgery, Niigata University Graduate School of Medical and Dental Sciences
Kawori KOHGA	Department of Obstetrics and Gynecology, Graduate School of Medicine, the University of Tokyo
Takafumi KAWANO	Department of Pediatric Surgery, Research Field in Medicine and Health Sciences, Kagoshima University
Ryoko HARADA	Department of Nephrology, Tokyo Metropolitan Children's Medical Center
Tetsuji KANEKO	Clinical Research Support Center, Tokyo Metropolitan Children's Medical Center

(3) *Organizing a TG committee and secretariat*

Table 1 also shows the list of scientists on the TG committee, which was divided into three groups to develop separate the TGs for PC, CE, and MRKH.

The PC group comprised seven scientists: five pediatric surgeons and two pediatric urologists; the CE group comprised six scientists: one pediatric surgeon and urologist, three pediatric surgeons, and two pediatric urologists; and the MRKH group comprised five pediatric surgeons. The secretariat was located at the office of the research representative in the Department of Pediatric Surgery, Niigata University Graduate School of Medical and Dental Sciences.

(4) *Setting the scope of the CQs*

The title of the present TGs is "the appropriate transitional care of patients with PC, CE, or MRKH". Therefore, the common topics of the TGs for these three diseases are 'establishing the causal relationship between the decisions made for neonates and infants', and 'assessing the late consequences of the decisions made for neonates and infants with regard to the functional preservation of the genitourinary systems'. We also analyzed the current status of pregnancy and delivery in female patients and discuss the need for psychological support as an important issue for MRKH patients whose reproductive system is congenitally absent.

The CQs were set in the clinical algorithm of PC (Fig. 2), CE (Fig. 3), and MRKH (Fig. 4), respectively. The clinical algorithm describes the available treatments according to each patient's clinical status from birth to the AYA period. The CQs were designed to clarify the important clinical issues likely to occur in the course of treatment. Six CQs were prepared for PC and CE, and five CQs were prepared for MRKH (Table 2). The clinical significance of each CQ was evaluated using the PICO format (P: Patients, Problem, Population, I: Interventions, C: Comparisons, Controls, Comparators, and O: Outcomes), an example of which is shown in Table 3.

(5) *Performing a literature search and systematic review*

A literature search was performed by the Japan Medical Library Association (JMLA) using the following medical databases: the Cochrane Database of Systematic Reviews, PubMed, the Cochrane Library, and Igaku Chuo Zasshi (ICHUSHI) of the Japan Medical Abstracts Society (JAMAS), based on English or Japanese keywords derived from each PICO-formatted CQ.

Table 4 lists the scientists engaged in the systematic review. The Systematic Review Team members performed the first and second screening of the literature, evaluated and integrated the evidence, and wrote the Systematic Review reports. The strength of the body of evidence for each clinical outcome was evaluated according to the methods proposed by Minds [19] as follows: A (strong), B (moderate), C (weak), and D (very weak). Because neither clinical practice guidelines nor a systematic review was available in the selected literature for PC and CE, the overall evidence level integrated by the Systematic Review Team for each CQ was either C (weak) or D (very weak). The clinical outcomes were summarized in the clinical outcome sheets drafted by the systematic reviewers.

(6) *Developing recommendations*

To develop recommendations, we considered the balance between the advantages and disadvantages for the patients, the patients' diverse senses of value, and economic points. The recommendations and their strengths and weaknesses were itemized carefully by the TG committee members using the modified Delphi method, and a minimum of 70% agreement was required for a consensus. Revisions of the recommendations or their strengths that did not achieve a consensus were discussed twice. If a consensus was not achieved after these procedures, the recommendation or its strength was not established and if a recommendation could not be obtained, the committee's comment was introduced. A summary of the systematic review leading to the

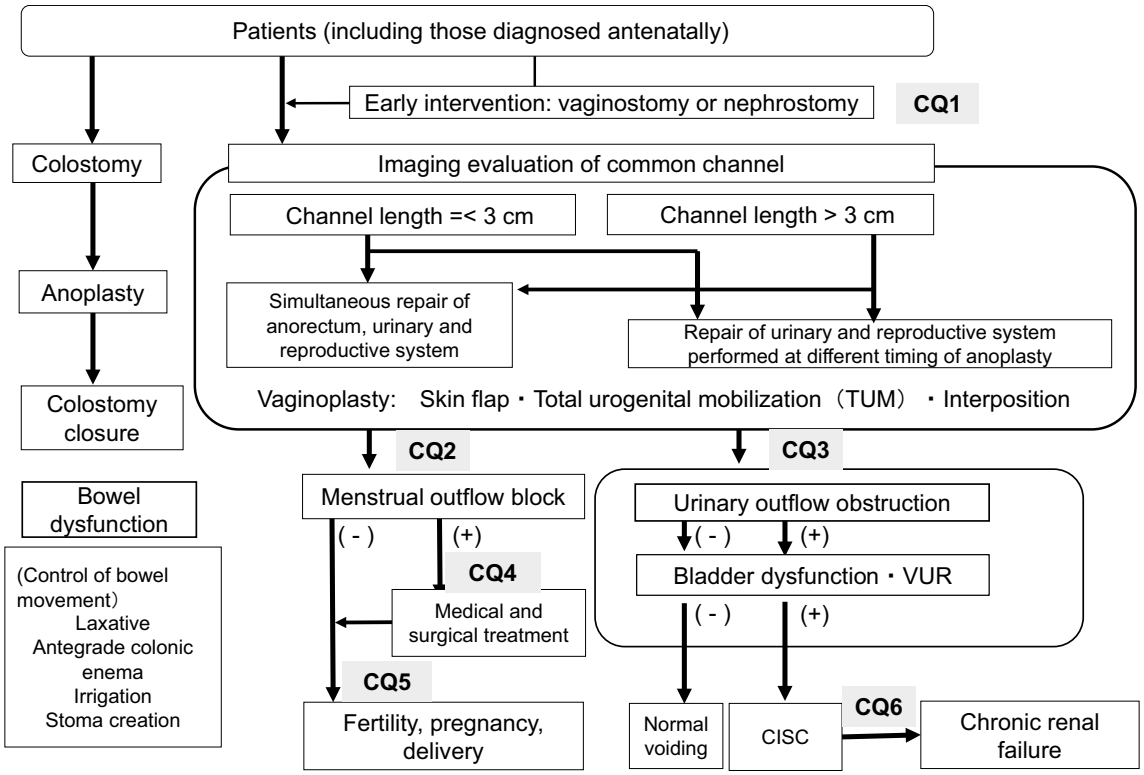

Fig. 2 Treatment algorithm of persistent cloaca (PC) and clinical questions (CQs)

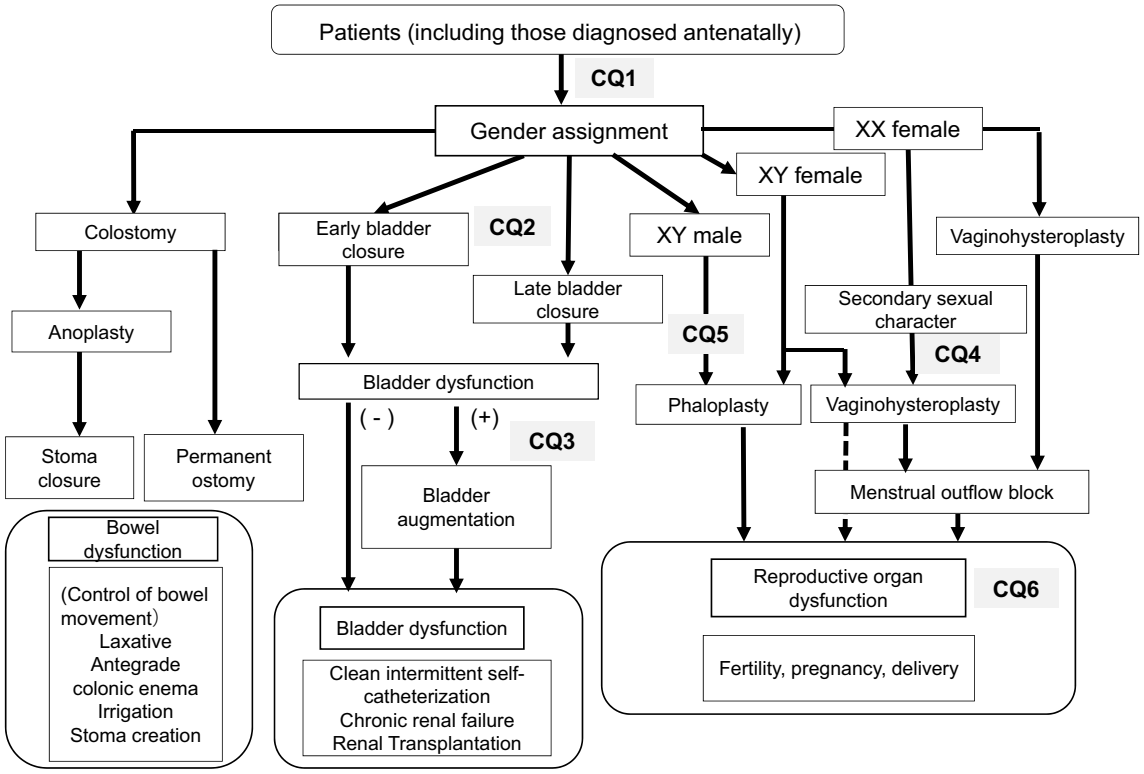

Fig. 3 Treatment algorithm of cloacal exstrophy (CE) and clinical questions (CQs)

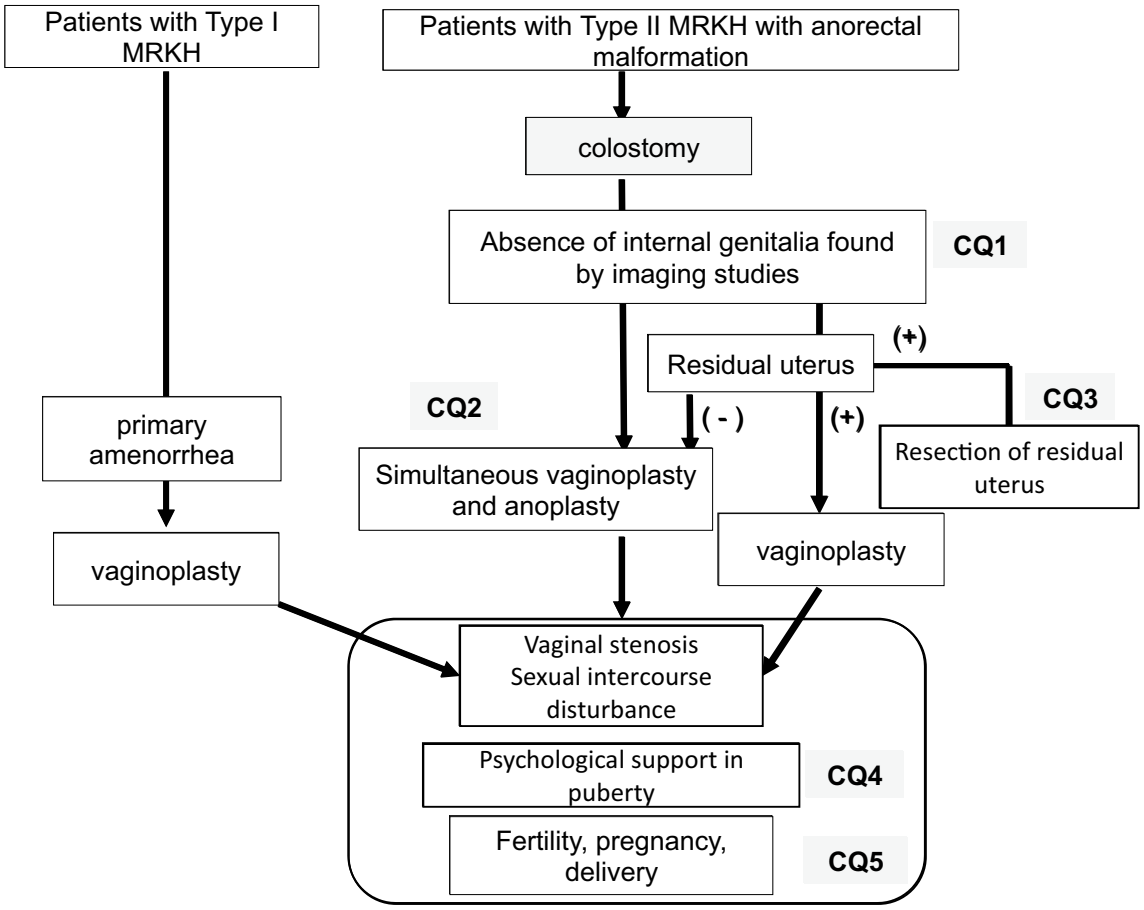

Fig. 4 Treatment algorithm of Mayer–Rokitansky–Küster–Häuser syndrome (MRKH) and clinical questions (CQs)

recommendations was described, and the important issues were considered when making recommendations, such as the strengths and limitations of the adopted studies. Applications in health insurance were also added.

(7) *Writing the first draft of the TGs*

The first draft of the TG for PC, CE, and MRKH in Japanese was completed in 2015, including the organization and development process, scope, recommendations, activities after release, and appendix (collected evidence data).

(8) *Performing an external evaluation and obtaining public comments*

An external evaluation was performed by two established pediatric surgeons and one scholar in the Department of Health Policy according to the AGREE II (https://www.agreetrust.org/agree-ii/). Public comments on the TG draft were collected from the Japanese Association of Pediatric Surgeons (JSPS), the Japan Society of Obstetrics and Gynecology (JSOG), the Japan Society of Perinatal and Neonatal Medicine (JSPNM), the Japanese Society of Pediatric Urology (JSPU), and the Japanese Society of Pediatric Nephrology. Revised TGs were prepared, taking into consideration the results of the above evaluations, and the final version of the TGs was approved by the TG committee in 2016, two academic societies (JSPS and JSPU) in 2017, and Minds in 2018.

(9) *Releasing the TGs*

The present TGs for PC, CE, and MRKH were presented by the research representative as a keynote lecture at the 24th Congress of the Asian Association of Pediatric Surgeons in May, 2016, in English, and at the educational lecture of the 52nd Annual Meeting of JSPNM in July, 2016, in Japanese. A practical version of the TGs in Japanese was published in book format in March 2017 [20]. The full and practical versions of the TGs in Japanese have been available on the website of JSPS, for members to download since May 2017 (full version: http://www.jsps.gr.jp/img/member/mjgruv/ and as a practical version: http://www.jsps.gr.jp/img/member/m8c50e/). The full version of the TGs, in Japanese, was also made available on the website of Minds for public download (https://minds.jcqhc.or.jp/guide_author/info_detail/T0012409) in April 2018.

Table 2 List of clinical questions (CQs) about persistent cloaca (PC), cloacal exstrophy (CE), and Mayer–Rokitansky–Küster–Häuser syndrome (MRKH)

Six CQs about PC	
CQ1	Is surgical treatment of hydrometrocolpos or hydronephrosis useful for preventing chronic renal failure?
CQ2	Does the selection of a surgical strategy according to the length of the common channel improve menstrual outflow block?
CQ3	Does the selection of a surgical strategy according to the length of the common channel improve urinary voiding dysfunction?
CQ4	Is medication for menstrual outflow block useful?
CQ5	Are pregnancy and delivery possible?
CQ6	Is clean intermittent self-catheterization (CISC) useful for preventing chronic renal dysfunction?
Six CQs about CE	
CQ1	Should decisions regarding whether to raise patients as a boy or girl be made based on the results of sex chromosomes?
CQ2	Is early closure of bladder useful for the preservation of bladder function?
CQ3	Does bladder augmentation with a urinary conduit improve the patients' quality of life?
CQ4	Should surgical reconstruction of the vagina and uterus be performed when secondary sex characteristics appear?
CQ5	Is the quality of life of the patient improved by reconstruction of the male external genitalia?
CQ6	Are pregnancy and delivery possible?
Five CQs about MRKH	
CQ1	Is a laparoscopic examination necessary for a definite diagnosis?
CQ2	Is vaginal reconstruction before puberty in patients with Type II MRKH associated with anorectal malformation useful?
CQ3	Should the rudimentary uterus be resected in childhood?
CQ4	Is psychological support necessary?
CQ5	Are pregnancy and delivery possible?

Table 3 PICO format for persistent cloaca (PC) clinical question (CQ) 1

Key clinical issue

Important clinical issue 1. hydrometrocolpos, hydronephrosis:
There are neonatal PC patients who need vaginostomy or nephrostomy immediately after birth. Such surgical intervention may affect the long-term outcomes of fertility and bladder function, making it still a matter of debate.

Component of CQs

P (patients, problem, population)

Sex	Female
Age	Not specially determined
Pathology	Persistent cloaca
Geographic component	Not specially determined
Associated condition	Hydrometrocolpos, hydronephrosis

I (Interventions)/C (comparisons, controls)

Surgical intervention of vesicostomy or vaginostomy

List of outcomes	Outcome	Benefit/harm	Score of importance	Adoption of outcome
O1	Improvement of voiding dysfunction	Benefit	4	Not
O2	Improvement of bladder dysfunction	Benefit	4	Not
O3	Prevention of chronic renal failure	Benefit	8	Adopted

Clinical question 1

Is surgical treatment of hydrometrocolpos or hydronephrosis useful for preventing chronic renal failure?

Table 4 Systematic review committee

Chief: Yoshiaki KINOSHITA	Department of Pediatric Surgery, Niigata University Graduate School of Medical and Dental Sciences
Systematic review: persistent cloaca	
Shigeharu AOI	Department of Pediatric Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine
Yuhki ARAI	Department of Pediatric Surgery, Niigata University Graduate School of Medical and Dental Sciences
Eiji HISAMATSU	Department of Urology, Aichi Children's Health and Medical Center
Daisuke MATSUNO	Department of Urology, Chiba Children's Hospital
Kazunori TAHARA	Division of Pediatric Surgery, National Center for Child Health and Developement
Systematic review: cloacal exstrophy	
Kyoko MOCHIZUKI	Department of Surgery, Kanagawa Children's Medical Center
Junko MIYATA	Department of Pediatric Surgery, Graduate School of Medical Sciences, Kyushu University
Yuichi HASEGAWA	Division of Urology, National Center for Child Health and Development
Woo Jin KIM	Department of Urology, Kanagawa Children's Medical Center
Hajime KAWAKAMI	Department of Pediatric Surgery, University of Tsukuba
Systematic review team: Mayer–Rokitansky–Küster–Häuser syndrome	
Katsuji YAMAUCHI	Department of Pediatric Surgery, Nara Hospital, Kindai University Faculty of Medicine
Yasuhisa URITA	Department of Pediatric Surgery, University of Tsukuba
Keiko AINOYA	Department of Urology, Miyagi Children's Hospital
Nana AKINO	Department of Obstetrics and Gynecology, Graduate School of Medicine, the University of Tokyo
Katsuko EGASHIRA	Department of Gynecology and Obstetrics, Graduate School of Medical Sciences Kyushu University

Ethical considerations and grant support

The Institutional Ethics Committee of Niigata University School of Medicine approved the study protocol of the research project (approved number, 1888).

This research project of general-068, entitled "The establishment of treatment guidelines for the smooth transitional care of persistent cloaca, cloacal exstrophy, and Mayer–Rokitansky–Kuster–Hauser syndrome", was supported by Health and Labour Sciences Research Grants for Research on Rare and Intractable Diseases from 2014 to 2016 in Japan.

CQs and recommendations

Persistent cloaca

PC CQ 1.

1.1. Is surgical treatment of hydrometrocolpos or hydronephrosis useful for preventing chronic renal failure?

1.2. Recommendation: Proper surgical management of these pathologies should be performed according to each patient's condition, given the possibility that surgical management may ameliorate the progress of renal dysfunction (evidence level C, weak strength of recommendation).

1.3. Summary of evidence

The systemic review included five studies: four case studies [8, 9, 21, 22] and one cohort study [23]. Two of the four case studies reviewed the clinical outcomes of renal function [8, 21], one [8] revealed that renal dysplasia, vesicourethral reflux (VUR) or a renal scar might be predictive factors for future chronic kidney dysfunction (CKD), and one [21] showed no stage progression of CKD in patients with an initial CKD stage of 1–3 after 5 years of follow-up. Only one case study [8] described hydrometrocolpos and hydronephrosis, but details of surgical intervention were not mentioned. One cohort study [23] was designed to compare the surgical outcomes of PSARP and total urogenital mobilization (TUM) with regard to genitourinary outcome. Therefore, the effects of surgical intervention, such as vaginostomy or vesicostomy, on the preservation of renal function could not be evaluated.

1.4. Development of recommendation

Although the precise causal relationship of early surgical treatment of genitourinary pathologies to prevent CKD could not be established based on these studies, the progress of initial stage 1–3 CKD might be prevented by appropriate surgical treatment of hydrometrocolpos, hydronephrosis, and VUR. Patients with renal dysplasia, VUR, and a renal scar should be followed up closely for future occurrence of CKD. The percentage of agreement to the CQ1 recommendation by Delphi method was 19/25 (76.0%).

PC CQ 2.

2.1. Does the selection of a surgical strategy according to the length of the common channel improve menstrual outflow block?

2.2. Recommendation: no definite proposal could be made due to the lack of relevant literature

2.3. Summary of evidence

The systematic review included five studies: one systematic review [24], four case studies [7, 25–27], and one newly added case study [28]. When the incidence of menstrual outflow block in relation to the length of the common channel of the cloaca was examined, its incidence was suggested to be lower in patients with a short common channel and higher in those with a longer channel [7]. However, its relationship to the type of surgery was not elucidated due to a lack of precise information about the surgeries performed in two studies [25, 26] and lack of data on the common channel length in four studies [24–27]. Furthermore, in the patients with a long common channel, vaginoplasty seemed to be performed via laparotomy using relatively complex methods of vaginoplasty, such as vaginal flap, vaginal switch, and reconstruction with intestine or colon, but precise details were not mentioned.

2.4. Development of recommendation

The poor information concerning vaginoplasty hampered the elucidation of the relationship between menstrual outflow block and the type of operation in patients with short or long common channels. One study [25] suggested that asymmetrical anomaly of the vagina and uterus might be another factor associated with menstrual outflow block. Therefore, we were unable to make any solid recommendations for CQ2. However, it can neither be concluded nor excluded that the selection of a surgical strategy based on the length of the common channel improves the occurrence of menstrual outflow block.

PC CQ 3.

3.1. Does the selection of a surgical strategy according to the length of the common channel improve urinary voiding dysfunction?

3.2. Recommendation: no definite proposal could be made due to the lack of relevant literature.

3.3. Summary of evidence

The systematic review included three studies: one cohort study [23] and two case studies [9, 29]. In all three studies, the method of surgery was not changed according to the length of the common channel. Furthermore, the urological function after definitive surgery was not evaluated based on the type of surgery. In one case study [9], 40 of 50 PC patients had urinary continence. Voluntary urinary continence was observed in 8 (31%) of 26 patients with a common channel ≤ 3 cm in length, but in only 3 (12%) of 24 patients with a common channel > 3 cm in length. Similarly, a cohort study [23] of 42 patients who underwent either TUM or PSARP confirmed voluntary urinary continence in 84% of those with a common channel ≤ 3 cm in length, but in only 33% of those with a common channel > 3 cm in length.

3.4. Development of recommendation

The clinical outcomes of these three studies indicate a trend toward a better clinical outcome in patients with a common channel ≤ 3 cm in length with regard to either spontaneous urinary voiding or urinary continence using clean intermittent self-catheterization (CISC); however, a causal relationship between the clinical outcome and the type of operation could not be elucidated. Therefore, we were unable to make any solid recommendation for CQ3.

PC CQ 4.

4.1. Is medication for menstrual outflow block useful?

4.2. We cannot confirm the usefulness of medication versus surgical treatment for menstrual outflow block. However, appropriate medication should always be given (evidence level D, weak strength of recommendation).

4.3. Summary of evidence

The systematic review included five case studies [7, 26, 27, 30, 31]. Menstrual outflow block was detected in puberty in 36% of patients who underwent vaginoplasty in childhood, and 5% needed hysterectomy [27]. Surgical treatment was recommended for menstrual outflow block [26]. As conservative treatment, only hormonal therapy was used. Even though hormonal therapy ameliorated symptoms and inflammatory changes of the internal reproductive organs [26, 31], only one patient was managed without vaginoplasty.

4.4. Development of recommendation

Hormonal treatment cannot be used as a substitute for surgical treatment, but proper intervention with hormonal treatment is still recommended. The percentage of agreement to the CQ4 recommendation was 23/24 (95.8%) for the Delphi procedure.

PC CQ 5.

5.1. Are pregnancy and delivery possible?

5.2. Pregnancy and delivery are possible, but intensive care throughout the course of pregnancy and delivery is necessary for successful childbearing (evidence level C, weak strength of recommendation).

5.3. Summary of evidence

The systematic review included seven studies (five case reports [32–36] and two case studies in Japanese [37, 38]). Five case reports described vaginal delivery [32], right remnant tubal pregnancy [33], triplets [34], and deliveries after in vitro fertilization [35, 36]. Including the patients in the two case studies, 7 of 13 pregnant women were delivered of babies (one vaginal delivery, four deliveries by Caesarean section, and two unknown). There were two cases of natural conception and two cases of in vitro fertilization, but no information was available for nine cases. Concerning complications during pregnancy and delivery, one patient gave birth twice: Her first pregnancy was hampered by premature rupture of the membrane at 34 weeks of gestation, resulting in spontaneous delivery [32], while in the second pregnancy, premature rupture of the membrane occurred at 30 weeks of gestation, and emergency Caesarean section was performed to rescue triplets [34]. One patient suffered a urinary tract infection [35] that did not affect the pregnancy course, while another patient [36] who complained of abdominal pain in early pregnancy suffered a urinary tract infection at 27 weeks of gestation and premature rupture of the membrane at 28 weeks of gestation, so emergency Caesarean section was performed.

There were no reports that denied the possibility of pregnancy and delivery in PC patients. Conversely, it was mentioned that pregnancy seemed possible in all seven patients seen at 16–23 years of age [37]. However, it was suggested that a vaginal delivery might lead to destruction of the previous vaginoplasty, so Caesarean section was the delivery of choice [32].

5.4. Development of recommendation

PC patients usually undergo multiple laparotomies for constructive surgery of the anus and genitourinary system from childhood. Therefore, careful preoperative consultation between the patient and an experienced obstetrician who understands the patient's genitourinary and abdominal condition is necessary for delivery by Caesarean section. However, the accumulation of further scientific data is needed before pregnancy and delivery can be strongly recommended in PC patients. The percentage of agreement to the CQ5 recommendation by the Delphi method was 11/15 (73.3%).

PC CQ 6.

6.1. Is CISC useful for preventing chronic renal dysfunction?

6.2. Because CISC is a useful tool for preventing urinary voiding dysfunction, early intervention using CISC is recommended (evidence level C, weak strength of recommendation).

6.3. Summary of evidence

The systematic review included three case studies [23, 38, 39]. The percentages of patients managed with CISC in each of the studies were 59% (25 of 42 patients) [23], 83% (8 of 11 patients) [39], and 33% (5 of 15 patients) [38]. Four of the 19 patients (21%) with a short common channel and 3 of the 6 patients (50%) with a long common channel were managed with CISC [23]. Renal transplantation was performed in one patient with a short common channel and in one with a long common channel [23]. It was also noted that patients with a long common channel had a higher incidence of urinary tract infection, and the ratio of patients with voluntary urinary control was low [23]. Two of 15 patients required hemodialysis [38]. All patients with a long common channel had urinary voiding dysfunction [38].

6.4. Development of recommendation

There is a percentage of patients with urinary tract infection or urinary voiding dysfunction, especially among those with a long common channel. Although there is no direct evidence supporting the ability of CISC to prevent chronic renal dysfunction, controlling urinary voiding with CISC might eliminate the risk factors for chronic kidney dysfunction. The percentage of agreement to the CQ6 recommendation by the Delphi method was 18/21 (85.7%).

Cloacal exstrophy

CE CQ 1.

1.1. Should decisions be made about whether to raise children as boys or girls based on the results of sex chromosomes?

1.2. It has been proposed that 46 XY children with CE be raised as boys, but agreement among the concerned parties must be made beforehand (evidence level C, recommendation grade could not be defined by the Delphi method).

1.3. Summary of evidence

This review included four studies: two cohort studies [40, 41] and two case studies [12, 42]. The four studies included a collective 25 genetic females and 76 genetic

males whose gender assignment was female in 58 and male in 18. When gender assignment was determined in accordance with sex chromosomes, there was no conflict in gender identity among either the genetic females or males, although there were male patients who were dissatisfied with their compromised external genitalia [12]. When genetic males were raised as girls, it was reported that 55% requested sex reversal [40]. In one study, none of three genetic males raised as girls requested sex reversal, but masculinization of their characteristics was reported [42]. It was acknowledged in four studies that the fetal male brain was imprinted as male because of the androgen shower. Correspondingly, one study suggested gender assignment in accordance with sex chromosomes [40], while another suggested that genetic males should be raised as girls because of the poor development of their external genitalia [12]. It was also suggested that psychosocial support is mandatory when genetic males are raised as girls [42]. According to referral data on the doctors' opinion, a nationwide survey of pediatric urologists, fellows of the American Academy of Pediatrics, reported that 79% of fellows favored male gender assignment for genetic male patients [43].

1.4. Development of recommendation

Given these collective findings, we concluded that gender assignment for genetic male patients should be decided with cautious consideration of their social and private backgrounds. The percentage of agreement for strong or weak recommendation to the CQ1 by the Delphi method was equally separated into 11/22 (50%) in four procedures. Therefore, a recommendation grade could not be defined.

CE CQ 2.

2.1. Is early closure of the bladder useful for the preservation of bladder function?

2.2. No definite proposal could be made due to the lack of relevant literature.

2.3. Summary of evidence

This review included four case studies [12, 44–46]. It was suggested that normal bladder function could not be expected after reconstructive surgery of eviscerated bladders [46]. Therefore, evidence was reviewed concerning factors for favorable outcomes after bladder closure. Among 23 patients who underwent primary closure of the bladder within 48 h after birth, bladder augmentation was performed later in 13 (57%) at between 3 and 6 years of age [44]. When 60 patients were divided into two groups according to failure or success of bladder closure, the average age at operation was 2 days and 15 months in the failure and success groups, respectively, favoring late closure [45]. It was also reported that urinary continence after bladder neck reconstruction was observed in 40% of patients without spinal anomalies, but in only 7% of patients with spinal anomalies [44].

2.4. Development of recommendation

Evidence indicating that early bladder closure is superior to late bladder closure with regard to retention and voiding of urine is lacking. Therefore, these results do not support the superiority of early bladder closure over late bladder closure.

CE CQ 3.

3.1. Does bladder augmentation with a urinary conduit improve the QOL?

3.2. It has been proposed that bladder augmentation with a urinary conduit can improve the patient QOL (evidence level C, weak strength of recommendation).

3.3. Summary of evidence

This review included two case studies [12, 47]. Bladder augmentation and closure of the bladder neck with a urinary conduit or bladder neck reconstruction achieved urinary continence in 40 (73%) of 55 patients [47]. The incidences of urinary continence were 88% (29 of 32 patients), 50% (7 out of 14 patients), and 89% (32 out of 39 patients) after bladder neck closure, bladder neck reconstruction, and bladder augmentation, respectively [47]. In another study, surgery for urinary continence was performed in 40 patients, as bladder neck construction in 21, bowel nipple in 7, and bladder neck obstruction with a urinary conduit in 12, achieving overall continence of 78% [12]. Although bladder augmentation was performed in 88% of the patients, the details of combined surgery and clinical results were not described.

3.4. Development of recommendation

These results suggest that urinary continence operations are performed in combination with bladder augmentation in most patients, which might contribute to the high success rate of urinary continence by reducing the bladder pressure and increasing its capacity. The percentage of agreement to the CQ3 recommendation by the Delphi method was 15/22 (71.4%).

CE CQ 4.

4.1. Should surgical reconstruction of the vagina and uterus be performed when secondary sex characteristics appear?

4.2. No definite proposal could be made due to the lack of relevant literature.

4.3. Summary of evidence

This review included four case studies [10–12, 48]. Collected case data from these four studies revealed that vaginoplasty was performed without using organ substitutes in 32 patients, and with different organ substitutes for vagina in 27 patients. The ileum was used in 16 patients, colon in 6, bladder in 4, and mega-ureter in 1. In 7 patients who underwent vaginoplasty at 5–8 years of age, hematometra was observed at 11–16 years of age in both the patients with ileal substitute and in three of four patients with bladder substitute [48]. Vaginoplasty without an organ substitute was performed in one patient, who did not suffer hematometra [48]. Among 14 patients who underwent vaginoplasty without organ substitute, one required total hysterectomy for hematometra and one required hemi-hysterectomy followed by resection of the remnant hemi-uterus following a tuboovarian abscess [11]. Vaginal stenosis was reported in a 26-year-old patient who had undergone vaginoplasty with bladder substitute at 14 years of age [48]. One case report documented that sexual intercourse was possible for a 23-year-old patient who had undergone vaginoplasty using an ileal substitute at 6 years of age and needed re-anastomosis of the ileum and uterus at 14 years of age because of hematometra [48]. Similarly, reports on four other patients [10, 11] described successful sexual intercourse, although details of the gynecological operations in these patients were not described. There was a report of pregnancy resulting in spontaneous abortion at 11 weeks of gestation in one patient [11]. These results suggest that the clinical outcome of vaginoplasty without an organ substitute is better than that with organ substitutes.

4.4. Development of recommendation

Therefore, vaginoplasty without an organ substitute before puberty might be the best treatment option. However, this is not still conclusive because of the lack of comparative data on the outcomes of vaginoplasty performed before and after puberty. It is recommended that constructive surgery of the vagina and uterus be performed at the appropriate time based on each patient's condition.

CE CQ 5.

5.1. Is QOL improved by reconstruction of the external genitalia in these men?

5.2. It has been suggested that reconstructive surgery of the male external genitalia may improve cosmetic satisfaction; however, the male sexual function cannot be recovered (evidence level D, weak strength of recommendation).

5.3. Summary of evidence

This review included four case studies [10, 12, 49, 50]. The collected case data from these four studies yielded 47 genetically male patients: 27 raised as girls and 20 raised as boys. Construction of the external genitalia was performed in 14 patients. It was reported that two of four patients who entered puberty had erectile dysfunction. One of these two patients was unable to engage in sexual intercourse due to the shortness of his penis, while the other patient was married and able to have sexual intercourse [50]. These two patients with erectile function had a normal sperm count and mobility, but pregnancies in their partners were not reported. This study suggests that pregnancy of the partners of these patients might be possible by in vitro fertilization.

Reconstruction of the external genitalia was performed in eight patients, but the constructed penis was always very short (roughly −2 standard deviations) [50]. Urethro-cutaneous fistula and intractable urethral stenosis developed in one patient each, respectively. Radial forearm free flap phalloplasty for penile inadequacy resulted in good cosmetic satisfaction as well as a good penile sensation. Tissue necrosis and neuroma in the forearm were reported as early complications but no late complications were reported [49].

5.4. Development of recommendation

A new technique of radial forearm free flap phalloplasty might be a promising method of penile reconstruction, but it is too early to conclude whether this technique will increase the QOL of these patients. The percentage of agreement to the CQ5 recommendation by the Delphi method was 17/21 (81.0%).

CE CQ 6.

6.1. Are pregnancy and delivery possible?

6.2. Pregnancy and childbearing are possible but cannot be readily recommended (evidence level D, weak strength of recommendation).

6.3. Summary of evidence

This review included three studies: two case studies [11, 51] and one case report [52]. One of the case studies reported that a patient who underwent only resection of the vaginal septum or hemi-vaginectomy of a double vagina without any operation on the uterus became pregnant but aborted at 11 weeks of gestation [11]. Another case study reported that one of three patients in puberty became pregnant and was delivered of a baby through Caesarean section [51]. During the Caesarean section procedure, rupture of the ileal pouch occurred, and prolapse of the uterus was observed after the operation. The case report [52] described a 21-year-old patient with a natural pregnancy who was delivered of a baby though Caesarean section after careful management of her pregnancy course from 20 to 36 weeks of gestation. This patient had a unicorn uterus with a duplicated

cervix and double vagina, and the left ovary and tuba were absent. This patient underwent closure of the bladder with stoma formation, followed later by bladder augmentation with ileal conduit when she was 17 years of age. Anoplasty was performed by the PSARP method at 2 years of age. In the Caesarean section operation, a long midline abdominal incision was necessary due to intra-abdominal adhesions and the presence of an augmented bladder and ileal conduit.

6.4. Development of recommendation

There are a few reports of 46 XX patients who became pregnant and bore a child. Because of the risk of grave complications of the gastrointestinal and urinary tract during pregnancy and delivery, meticulous care is required throughout the course of pregnancy and delivery. Therefore, childbearing is not recommended because of the severe risks of morbidity associated with pregnancy and delivery. The percentage of agreement to the CQ6 recommendation by the Delphi method was 18/21 (85.7%).

Mayer–Rokitansky–Küster–Häuser syndrome

MRKH CQ 1.

1.1 Is laparoscopic examination necessary for a definite diagnosis?

1.2. No definite proposal could be made due to the lack of relevant literature.

1.3. Summary of evidence

This review included two cohort studies [53, 54]. On comparing laparoscopic examinations with examinations by magnetic resonance imaging (MRI) or ultrasonography, the diagnostic accuracy of laparoscopy was found to be superior to that of MRI or ultrasonography for detecting internal reproductive organ pathologies [53]. However, the vagina and cervical regions of the uterus could not be seen laparoscopically, so MRI was recommended for those regions. Among 56 patients (14–30 years of age) who had been diagnosed by MRI, 41 underwent a preoperative laparoscopic examination. The accuracy of MRI for making a diagnosis was 100% in sensitivity, but the detection rate of Müllerian buds was 81.4% ($\kappa = 0.55$, fair) [54].

1.4. Development of recommendation

A laparoscopic examination is recommended for patients with amenorrhea after puberty whose definite diagnosis cannot be obtained with MRI. However, indications are difficult to identify on a laparoscopic examination for prepubescent pediatric patients.

MRKH CQ 2.

2.1. Is vaginal reconstruction before puberty in patients with Type II MRKH associated with anorectal malformation useful?

2.2. No definite proposal could be made due to the lack of relevant literature.

2.3. Summary of evidence

This review included five case studies [55–59]. Eight patients with Type II MRKH associated with ARM underwent vaginoplasty using an organ substitute (distal colon) at 2 months of age. Two of the eight patients grew to puberty, and sexual intercourse was reported to be possible for one patient [56]. In a study of 20 patients who underwent vaginoplasty simultaneously with anoplasty, vaginoplasty was performed using organ substitutes of the distal rectum in 12, sigmoid colon in 6, and terminal ileum in 2, but the long-term follow-up status was not documented [56]. In a study of seven patients [59], vaginoplasty was also simultaneously performed with anoplasty.

2.4. Development of recommendation

These studies suggested that the staged operation of vaginoplasty after anoplasty might be disturbed by intestinal adhesion. Therefore, vaginal reconstruction before puberty should be considered as surgical treatment for Type II MRKH associated with ARM, but the ideal timing of vaginoplasty is still unclear.

MRKH CQ 3.

3.1. Should the rudimentary uterus be resected in childhood?

3.2. Resection of the rudimentary uterus should not be performed in childhood (evidence level C, weak strength of recommendation).

3.3. Summary of evidence

This review included three case series [60–62] and two case reports [63, 64]. Among 48 patients, a rudimentary uterus was found in 23 (48%). The relative risk of pelvic pain after puberty was 2.33 times higher than in patients without a rudimentary uterus [61]. When endometrium was found in the rudimentary uterus by MRI, this risk increased to 3.57, whereas it dropped to 1.53 when endometrium was not detected by MRI [61]. Resection of the rudimentary uterus was performed in nine patients with pelvic pain, and the symptoms disappeared postoperatively in all patients [61]. The usefulness of hormonal treatment for pelvic pain was also reported [60, 61].

3.4. Development of recommendation

These results suggest that endometrium in the rudimentary uterus might induce hydrometra or endometriosis in puberty caused by dissemination of the endometrium during the back-flow of menstrual blood. However, the presence or absence of endometrium in the rudimentary uterus cannot be evaluated before puberty. Therefore, no reasonable rationale for resecting the rudimentary uterus in children could be found. The percentage of agreement to the CQ3 recommendation by the Delphi method was 18/21 (85.7%).

MRKH CQ 4.

4.1. Is psychological support necessary?

4.2. Proper intervention with psychological support is recommended (evidence level C, strong strength of recommendation).

4.3. Summary of evidence

This review included four cohort studies [65–68], one review study [69], and two additional studies (a case study [70] and randomized controlled trial [71]). Patients appear to encounter two major problems on entering puberty. One is the need for vaginoplasty or dilatation of the vagina to enable comfortable sexual intercourse. Another is psychological support when they learn of their disability concerning sexual intercourse and childbearing. Four studies [65–68] evaluated the QOL of patients after vaginal reconstruction using different scoring systems. Interestingly, these studies suggested that spiritual or sexual satisfaction was not achieved, even if surgery was successful. It was also pointed out that patients whose vaginal length was longer than 4.5 cm had more sexual activity, but psychological anxiety was higher in patients who underwent vaginoplasty [65].

Awareness of their physical disability poses a heavy psychological burden on these patients, who cannot easily accept that they may be unable to have normal sexual intercourse and bear children, which injures their self-respect and evokes resentment of other women. Although the need for psychological support is well recognized, no effective treatment approach has been proposed. The usefulness of group intervention [69] was recently reported and has since come to be known as "cognitive-behavioral group intervention" [70, 71]. The usefulness of this approach was demonstrated in a randomized controlled trial [71].

4.4. Development of recommendation

These studies show the value of psychological support for patients with MRKH syndrome. The percentage of agreement to the CQ4 recommendation by the Delphi method was 14/20 (70.0%).

MRKH CQ 5.

5.1. Are pregnancy and delivery possible?

5.2. No definite proposal could be made due to the lack of available means of childbearing for these patients in Japan.

5.3. Summary of evidence

This review included four studies: three case series [72–74] and one case report [75]. Surrogate in vitro fertilization was performed in 27 patients [72], 6 patients [73], and 2 patients [74]. One patient underwent uterus transplantation before in vitro fertilization [75]. These studies pointed out that the collection of ovarian follicles was performed laparoscopically or via laparotomy instead of via a transvaginal approach due to the anatomical deviation of the ovaries. To carry out surrogate in vitro fertilization, ethical, legal, and medical aspects must all be considered [74]. In Japan, surrogate in vitro fertilization is not prohibited because it has not been discussed as an issue of legal restriction, but the JSOG and the Ministry of Labor and Welfare do not support it. Furthermore, the surrogate mother is recorded as the legal mother of the baby in Japan, so adoption procedures must be carried out to establish a legal relationship between the mother and child.

Uterus transplantation is another method of surrogate in vitro fertilization. A 35-year-old patient underwent transplantation of the uterus from a postmenopausal 61-year-old donor [75] after in vitro fertilization 1 year earlier. Immunosuppression was maintained during the course of pregnancy, and a baby weighing 1775 g was born by Caesarean section because of pregnancy-induced hypertension at 31 weeks and 5 days of gestation. Even though this patient with uterus transplantation successfully achieved pregnancy and delivery, this treatment modality is still experimental.

5.4. Development of recommendation in consideration of social circumstances in Japan

It is possible to have a child through surrogate birth or uterus transplantation; however, neither of these modalities are allowed at present in Japan. Therefore, there is no practical available method for these patients to bear children yet in Japan.

Discussion

To our knowledge, no TGs have been published for the smooth transitional care of patients with PC, CE, or MRKH from infancy to adulthood. Therefore, in the present TGs, MRKH patients were limited to those who had been diagnosed coincidentally in childhood as a result of associated anomalies or diseases. This research project was carried out

from 2014 to 2016 in Japan. Before developing the TGs, a nationwide survey of patients with PC, CE, or MRKH was conducted in 2014 to obtain basic information about these anomalies [1] (data on MRKH were not published). Responses were obtained from 113 institutions on a collective total of 466 cases of PC, 229 cases of CE, and 21 cases of MRKH, which amounted to the total number of patients treated in the past. According to the annual registry data of the Japanese Study Group of Anorectal Malformation [76], 1992 patients with ARM were registered between 1976 and 1995. In this study, there were 93 (4.7%) patients with PC and 12 (0.6%) with CE. The number of patients reported in the nationwide survey was larger than that in the registry data, probably due to differences in the study periods and number of institutions involved (113 institutions in the nationwide survey vs. 50 institutions in the registry).

In the TGs for PC, hydrometrocolpos and hydronephrosis in neonates (CQ1), the effects of surgery according to the length of the common channel on menstrual outflow block (CQ2) and the urinary voiding function (CQ3), medication for menstrual outflow block (CQ4), pregnancy and delivery (CQ5), and the effects of CISC on renal function (CQ6) were selected as topics. In the nationwide survey in Japan [1], 90% of PC patients had some anomaly of the internal genitalia. A double uterus (50.0%) or double vagina (35.2%) was the most frequent, followed by retention of fluid, such as hydrocolpos (23.6%), hydrometra (23.6%), and hydrosalpinx (5.4%). Hydronephrosis and renal hypoplasia were also found in 29.1% and 15.5% of the patients, respectively. Therefore, hydrometrocolpos and hydronephrosis are important clinical issues to consider for surgical treatment in the neonatal period (CQ1). Among 178 PC patients with menstruation, a menstrual disorder, menstrual outflow block, volume disorder, and cycle disorder were observed in 35.4%, 22.5%, 31.4%, and 42.1%, respectively [1]. Menstrual outflow block in puberty is a serious problem that requires immediate surgical intervention or medication. It has been reported that patients with a short common channel had better surgical outcomes for menstrual outflow block [7] and urinary continence [9] than those with longer channels. However, the precise relationship between the surgical strategy and menstrual outflow block or urinary voiding function has not been elucidated. Thus, we reviewed the ideal surgical strategy according to the length of the common channel and its effects on menstrual outflow block (CQ2) or the urinary voiding dysfunction (CQ3); however, there were insufficient relevant studies to allow us to make a precise statement about CQ2 and CQ3. Future studies on the treatment of PC patients in puberty, the type of surgery, and length of the common channel will provide more clarity.

In the TGs for CE, gender assignment (CQ1), timing of bladder closure and bladder function (CQ2), impact of bladder augmentation (CQ3) and reconstruction of the male external genitalia on the QOL of patients (CQ5), timing of reconstructive surgery of the vagina and uterus (CQ4), and pregnancy and delivery (CQ6) were selected as topics. Gender assignment in genetically male patients leads to various life-long problems, depending on whether the patient is raised as a boy or a girl. When 46 XY patients were raised as girls, about half of the patients requested sex reversal in adulthood [40], while those who were raised as boys experienced severe psychological damage due to their severely compromised external genitalia and sexual function. Pediatric urologists in the United State generally seem to support the principle of male gender assignment in 46, XY patients [43]. However, this must still be considered carefully, as there is still no ideal method of reconstructive surgery of the male external genitalia. In a nationwide survey in Japan [1], a vesical operation was performed in 80.8% of CE patients, with primary closure of the bladder in 69.1% of them. Bladder augmentation was performed in 27.0% of CE patients. We expected that early bladder closure would have a favorable effect on bladder capacity (CQ2), but this was not demonstrated. However, bladder augmentation had a favorable effect on QOL in the systematic review in CQ3. We examined the timing of reconstructive surgery of the vagina and uterus in CQ4. A systematic review revealed a trend toward a better clinical outcome in those who underwent vaginoplasty without an organ substitute, but data from relevant studies according to the timing of vaginoplasty and clinical consequence are lacking, hampering any conclusive recommendation.

Pregnancy and delivery are the most important clinical issues for both PC and CE 46, XX patients; however, there have been only a few reports on this issue, as documented in the summaries of PC CQ5 and CE CQ6. According to a nationwide survey in Japan, 17 PC patients and 5 CE patients had married, and 4 of the PC patients but none of the CE patients had children [1]. The risks associated with pregnancy and delivery are much higher in CE 46, XX patients than in PC patients. Previous abdominal surgery in CE patients poses a high risk of serious complications throughout the course of pregnancy and delivery. Therefore, pregnancy and delivery are recommended only conditionally in PC but not at all in CE.

In the TGs for MRKH, laparoscopic examination of the internal genitalia (CQ1), vaginal reconstruction before puberty (CQ2), resection of the rudimentary uterus in childhood (CQ3), psychological support (CQ4), and pregnancy and delivery (CQ5) were selected as topics. Because MRKH is the main disorder associated with primary amenorrhea, the diagnosis is usually made in adolescence, and rarely in childhood. A nationwide survey of MRKH patients in Japan yielded only 21 patients, whereas 466 PC patients and 229 CE patients were accumulated in the same survey. Correspondingly, MRKH studies have primarily focused on adult

patients. We were able to review important evidence from studies of adults, some of which could be extrapolated to children (CQ3). However, we obtained no direct evidence to support recommendations in CQ1 and CQ2. Psychological support for MRKH patients is important and cognitive–behavioral group intervention [70, 71] appears to be a promising treatment modality (CQ4). The alternative methods of achieving pregnancy and delivery for patients such as those with MRKH without their own internal reproductive organs are not available in Japan, so no recommendation could be made.

During the present review process to develop TGs for PC, CE, and MRKH, it became apparent that current treatments for gynecological and urological anomalies in PC and CE patients are published mainly as case studies, meaning that surgical treatments are performed on an institutional basis. Furthermore, even in a large case series, vital information needed to evaluate the usefulness of a certain surgical treatment regarding the late clinical consequences on the gynecological and urological function is often lacking. The complexity of the inborn anomalies of PC and CE patients and the substantial inter-individual variation of anomalies might underlie this issue. Due to the rarity of MRKH diagnosed in childhood, the clinical findings obtained from the present review process to draft TGs for PC and CE might be useful for assessing the outcomes of vaginal reconstruction in childhood for MRKH patients. The most important issues to address in future studies on PC and CE are the description of both patterns of anomalies and choices of surgical treatment, especially according to the length of the common channel in PC patients.

Compliance with ethical standards

Conflict of interest Masayuki Kubota and his co-authors have no conflicts of interest to declare.

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Affiliations

Masayuki Kubota[1,2] · Yutaka Osuga[1,3] · Kiyoko Kato[1,4] · Kenji Ishikura[1,5] · Kazunari Kaneko[1,6] · Kohhei Akazawa[1,7] · Takeo Yonekura[1,8] · Yuko Tazuke[1,9] · Satoshi Ieiri[1,10] · Akihiko Fujino[1,11] · Shigeru Ueno[1,12] · Yutaro Hayashi[1,13] · Kaoru Yoshino[1,14] · Toshihiro Yanai[1,15] · Jun Iwai[1,16] · Takanori Yamaguchi[1,17] · Shintaro Amae[1,18] · Yuichiro Yamazaki[1,19] · Yoshifumi Sugita[1,20] · Miyuki Kohno[1,21] · Yutaka Kanamori[1,11] · Yuko Bitoh[1,22] · Masato Shinkai[1,23] · Yasuharu Ohno[1,24] · Yoshiaki Kinoshita[1,2]

1 Research Team for the Establishment of Treatment Guidelines for Persistent Cloaca, Cloacal Exstrophy and Mayer-Rokitansky-Küster-Häuser Syndrome for the Proper Transitional Care of the Patients, The Research Project for Rare and Intractable Diseases of the Ministry of Health, Labour and Welfare (MHLW), Tokyo, Japan

2 Department of Pediatric Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-Dori, Niigata 951-8510, Japan

3 Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

4 Department of Gynecology and Obstetrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

5 Division of Nephrology and Rheumatology, National Center for Child Health and Development, Tokyo, Japan

6 Department of Pediatrics, Kansai Medical University, Moriguchi, Japan

7 Department of Medical Informatics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

8 Department of Pediatric Surgery, Nara Hospital, Kindai University Faculty of Medicine, Ikoma, Japan

9 Department of Pediatric Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

10 Department of Pediatric Surgery, Research Field in Medicine and Health Sciences, Kagoshima University, Kagoshima, Japan

11 Division of Pediatric Surgery, National Center for Child Health and Development, Tokyo, Japan

12 Department of Pediatric Surgery, Tokai University School of Medicine, Isehara, Japan

13 Department of Pediatric-Urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

14 Department of Urology, Aichi Children's Health and Medical Center, Obu, Japan

15 Department of Pediatric Surgery and Pediatric Urology, Ibaraki Children's Hospital, Mito, Japan

16 Department of Pediatric Surgery, Chiba Children's Hospital, Chiba, Japan

17 Department of Urology, Fukuoka Children's Hospital, Fukuoka, Japan

18 Department of Surgery, Ekoh-Ryoikuen Hospital-homes for Persons with Severe Motor and Intellectual Disabilities (SMID), Sendai, Japan

[19] Department of Urology, Kanagawa Children's Medical Center, Yokohama, Japan

[20] Department of Urology, Kobe Children's Hospital, Kobe, Japan

[21] Department of Pediatric Surgery, Kanazawa Medical University, Kanazawa, Japan

[22] Department of Pediatric Surgery, Kobe University Hospital, Kobe, Japan

[23] Department of Surgery, Kanagawa Children's Medical Center, Yokohama, Japan

[24] Department of Gastroenterological and Pediatric Surgery, Oita University Faculty of Medicine, Oita, Japan