Anorectal Malformations

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Anorectal malformations (ARM) are a spectrum of congenital abnormalities of the terminal portion of the hindgut which lies partially or completely outside the anal sphincter mechanism. In these conditions, the gastrointestinal tract ends blindly or opens ectopically to the skin or the genitourinary tract (fistula). They affect about 1 in 5000 live births worldwide [1] with a slight male predominance. It is not always possible to correct completely these anomalies and long-term consequences with impacts on quality of life are frequent.

Classification

In 2005, an international conference for the development of standards for the treatment of ARM took place at Krickenbeck, Germany [2]. During this workshop, 26 international experts on congenital malformations of the organs of the pelvis and perineum reviewed the recent advances and developed an international classification for ARM (Table 29.1). The most frequent defects in male and female are, respectively, rectourethral fistula and vestibular fistula. In the past, the Wingspread classification subdivided the anomalies into low, intermediate, and high anomalies according to the level of the rectal pouchin relation to the levator ani muscles. This older classification is important to know in order to understand the older medical literature on the subject and to have an idea of the expected functional outcome: the highest the anomaly, the worst is the prognosis for fecal continence. Generally, ARM without perineal fistula are grouped under the high forms, and those with a perineal rectal opening are considered low forms [3] (Fig. 29.1a, b).

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Etiology

The etiology of ARM is unclear, but it is assumed to be multifactorial. In the animal models and human studies, genetic and environmental factors were identified. ARM have been induced in mice and rats by in utero exposure to Adriamycin, etretinate, and ethylenethiourea [4]. Some studies have suggested a link to in vitro fertilization [5] and maternal diabetes mellitus [6, 7]. No single gene or chromosomal locus has been identified. However, the frequent association with other congenital anomalies and genetic syndromes (Table 29.2) [8, 9] strongly supports a genetic component. Familial incidence has been shown in non-syndromic or isolated ARM, especially with the perineal and vestibular fistulas. Cloaca and rectoprostatic fistulae are less likely to have affected family members. The recurrence risk for rectovestibular and perineal fistulae is 3–4 % for full siblings and approximately 2 % for first-degree relatives [9].

Embryology

The embryology of many congenital anomalies in humans is still not completely understood and recent studies are questioning the traditional theories. ARM is an example and several animal models have been developed to better characterize it.

Abnormal development of the cloaca rather than a persistent stage of normal embryology is the hypothesis for most of the ARM [4]. In the normal embryo, the cloaca is formed around the third week of gestation. It consists of a common cavity into which the hindgut (rectum), the allantois (bladder), and the mesonephric ducts (Wolffian) open cranially. Caudally, the cloaca ends as the tail gut. The cloacal membrane extends vertically and anteriorly from the allantois to the tail gut. As a result of the ventral growth of the genital tubercle, the shape of the cloaca changes and the cloacal membrane swings to a horizontal position. A urorectal fold

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(or urogenital septum) situated between the allantois and the hindgut descents caudally until it meets the cloacal membrane. This descent results in the separation of the urethra and the rectum and in the disintegration of the cloacal membrane at that area (seventh week of gestation). The dorsal cloaca in the tail region remains fixed and will constitute the anal orifice. In ARM animal models, unusual shape of the cloaca, too short cloacal membrane (absent dorsal parts), and abnormal junction between the proximal hindgut and the cloaca were found (Fig. 29.2).

Table 29.1 International classification of anorectal malformations (Krickenbeck)

Major clinical groups	Rare regional variants
Perineal (cutaneous) fistula	Pouch colon
Rectourethral fistula	Rectal atresia/stenosis
(a) Bulbar	Rectovaginal fistula
(b) Prostatic	H fistula
Rectovesical fistula	Others
Vestibular fistula	
Cloaca	
No fistula	
Anal stenosis	

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The muscles surrounding the anorectum develop at the same time and are composed of three parts: the external sphincter, the puborectalis muscle, and the internal sphincter [10, 11]. The external sphincter appears first, followed by the puborectalis muscle which appears before 10 weeks of

Table 29.2 Syndromes with anorectal malformations

Syndrome/association	Genetic anomaly
VACTERL association	
Down	Trisomy 21
Patau	Trisomy 13
Edwards	Trisomy 18
Cat eye	Trisomy/tetrasomy 22
Townes-Brocks	Mutation of SALL1
Currarino	Mutation of HLXB9
Pallister Hall	Mutation of GLI3
X-linked heterotaxy	Mutation of ZIC3
Johanson-Blizzard	Mutation of UBR1
McKusick-Kaufman	Mutation of MKKS
Duane-radial ray/Okihiro	Mutation of SALL4
Bifid nose, anorectal, renal (BNAR)	Mutation of FREM1
Polydactyly, imperforation anus, vertebral (PIV)	

From Mundt E, Bates MD. Genetics of Hirschsprung disease and anorectal malformations. Semin Pediatr Surg. 2010;19(2):107–17, with permission

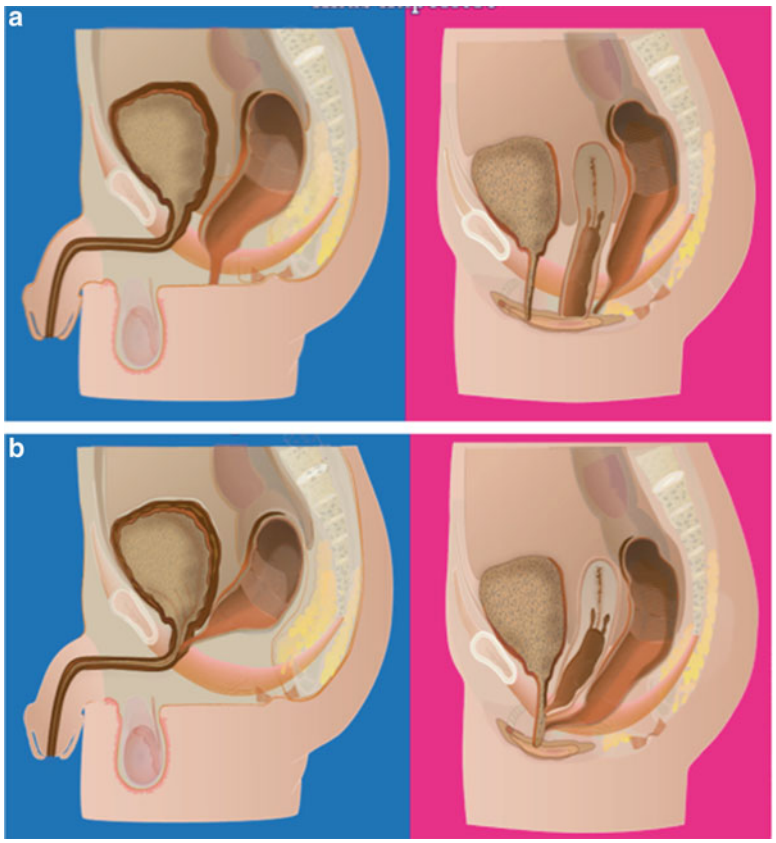

Fig. 29.1 (**a**) Schematization of perineal (male) and vestibular (female) fistula. (**b**) Schematization of rectourethral fistula (male) and cloaca (female). (From M Leduc, Medical Illustration, Sainte-Justine University Health Center, 2014, with permission)

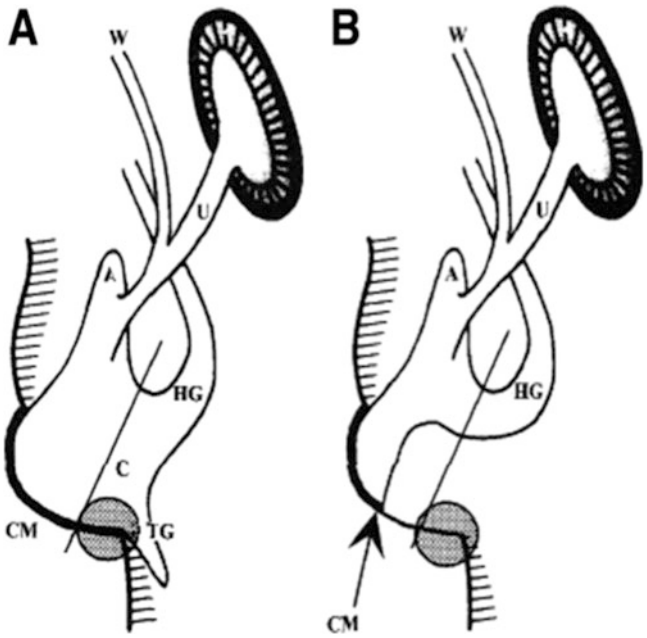

Fig. 29.2 Normal and abnormal cloaca. Schematic drawings of a normal (**a**) and an abnormal (**b**) cloaca. In the abnormal embryo, the cloacal membrane (CM) is too short (*arrow*). The cloacal membrane does not extend to the region of the tail groove (*gray area*). The dorsal cloaca is missing. In the normal embryo (**a**), the cloacal membrane is of normal length and extends to the region of the tail groove (*gray area*). (From Kluth D. Embryology of anorectal malformations. Semin Pediatr Surg. 2010;19(3):201–8, with permission)

gestation and forms a sling around the anorectum. The internal sphincter grows after the rupture of the cloacal membrane and is not well differentiated until 10 weeks.

Associated Malformations

More than 50 % of the newborns with ARM have at least one associated anomaly [12]. The higher forms are even more likely to have more other anomalies. The severity of these associated anomalies is variable from incidental findings to life-threatening conditions. ARM can be part of a syndrome in 3.7 %, a chromosomal anomaly in 11 %, a sequence in 9 % (caudal dysplasia, Potter syndrome, prune belly), or the VACTERL association (vertebral defects, anal atresia, cardiac septal defects, esophageal atresia, renal anomalies, and radial limb defect) in 10 % [8]. Abdominal wall defects, especially omphalocele (OEIS complex: omphalocele, exstrophy, imperforate anus, and spine anomalies), can be associated with anal anomalies in 6.8 %. Associated affected systems include cardiovascular, gastrointestinal, spinal, sacral, vertebral, genitourinary, and gynecologic. *Cardiovascular anomalies* need to be ruled out before the surgical management because they are present in 16–22 % of patients with ARM [13, 14], and they can change the initial management if significant. The most frequent anomalies are atrial septal defect and ventricular septal defect, but more significant malformations such as tetralogy of Fallot, transposition of great vessels, and hypoplastic left heart syndrome are also possible. Many *gastrointestinal anomalies* have been described; the most frequent are tracheoesophageal in 10 % and duodenal with or without malrotation in 1–2 %. Hirschsprung disease is rare in patients with ARM, and the diagnosis must be confirmed with certitude because of the increased risk of fecal incontinence if proctectomy is performed in a context of ARM. *Sacrovertebral anomalies* are the most frequent bony structures defects (hemivertebrae, scoliosis, hemisacrum) and affect about a third of the patients [15]. The co-occurrence of sacral defect (typically hemisacrum), ARM, and presacral mass (teratoma or anterior meningocele) is known as the Currarino triad [16]. It is autosomal dominant with variable expressivity. Hypodevelopment of the sacrum can be quantified by the sacral ratio which is a helpful prognostic tool for continence and is associated with the severity of the ARM [17]. The prevalence of *spinal anomalies* is about 50 % [18] with a wide variety of severity (thickened filum, fibrolipoma, tethered cord, syringomyelia, myelomeningocele). The clinical significance of the occult spinal dysraphism is unclear, but routine detection is recommended in all types of ARM [15, 19]. Untethering of the cord improves the motor function in symptomatic patients, but it does not change the bowel or urinary function [20]. Patients with tethered cord have a worse functional prognosis that is also predictable by the type of ARM and sacral defect, but there is no evidence that prophylactic surgery can change the prognosis [21]. Close clinical follow-up and urodynamic studies are recommended in patients with tethered cord [18]. *Genitourinary anomalies* affect one third to half of patients [22]. Vesicoureteral reflux is the most frequent anomaly, affecting 60 % [23], followed by renal agenesis and dysplasia. In males, 20 % have cryptorchidism [24] and 5 % have hypospadias [22]. Patients with ARM associated with partial sacral agenesis are at increased risk of bladder-sphincter dysfunction and should be assessed by urodynamic studies [25]. *Gynecologic anomalies* have been unrecognized in the past but constitute a significant cause of morbidity on the long term [26]. In girls with rectovestibular fistula, 5 % have a vaginal septum and 9 % an absent vagina [27]. Hydrocolpos can cause a urinary obstruction or pyocolpos in the neonatal period. The absence or underdevelopment of the Mullerian structures can cause obstruction of the menstrual flow at the puberty.

Neonatal Management

A thorough physical examination is of critical importance and will often lead to the diagnosis of the ARM and the associated anomalies [28]. When inspecting the perineum, it is

important to look at the color and aspect of the skin, assess the external sphincter contraction, and identify presence of ectopic anal opening. In boys, the presence of meconium at the meatus or in the urine will automatically confirm the presence of a rectourinary fistula. In girls, a single perineal orifice establishes the diagnostic of a cloaca. In this eventuality, it is mandatory to rule out hydrocolpos and urinary obstruction. In the cases where there is no visible meconium on physical examination, it is important to wait 24 h before labeling the type of anomaly and planning the surgical intervention. In the meantime, the baby should receive intravenous fluids, antibiotics, and nasogastric decompression. Associated anomalies must be ruled out by cardiac echography, renal and spinal ultrasound, and lumbar spine and sacrum plain radiographs. Within the first 24 h of life, if there is evacuation of meconium through a perineal fistula, a primary anoplasty can be performed. If the baby has other life-threatening issues, the fistula can be dilated and the definitive surgical treatment postponed for a few months as long as the rectum is well decompressed. If after 24 h there is no evidence of meconium in the urine or through a perineal fistula, a cross-table lateral radiograph can be performed with the baby in prone position and a marker at the suspected site of the external sphincter in order to assess the level of the rectal gas compared to the pubococcygeal line. A perineal ultrasound can also be performed. A distance between the distal rectal pouch and the perineum greater than 15 mm suggests an intermediate or high ARM [29].

Operative Management

The main goals of treatment in the neonatal period are to relieve the intestinal obstruction and recognize and treat any associated defects that may be life threatening [30]. Relieving the intestinal obstruction can be achieved by definitive repair, anal dilation, or colostomy. Depending on the experience of the surgeon and the patient clinical status, a low form without perineal fistula or a vestibular fistula can be primarily repaired or initially diverted by a colostomy. Some surgeons will also prefer to dilate the vestibular fistula and postpone the primary repair by few months when the plan between the vagina and the fistula has become thicker. A colostomy and delayed definitive repair at 2–3 months is recommended in higher forms (urethral fistula, cloaca) in order to characterize better the anatomy and prevent complications such as urethral injury. In cloaca, drainage of hydrocolpos and urinary diversion may be necessary. The distal colostogram is the best study to assess the anatomy [31]. A voiding cystourethrogram is also indicated to detect vesicoureteral reflux and, when done at the same time, can help to show the position of the rectal pouch compared to the urethra if no fistula is seen on the colostogram.

Table 29.3 International grouping (Krickenbeck) of surgical procedures for follow-up

Operative procedures	Perineal operation
	Anterior sagittal approach
	Sacroperineal approach
	PSARP
	Abdominosacroperineal pull-through
	Abdominoperineal pull-through
	Laparoscopy-assisted pull-through
Associated conditions	Sacral anomalies
	Tethered cord

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Operative Approaches of the Definitive Treatment

The main goal of the definitive treatment is to anatomically reconstruct the malformations in a way that will avoid complications that may lead to permanent sequelae. Table 29.3 enumerates the possible surgical procedures. Perineal operation is reserved for low forms. All ARM can be repaired by a posterior sagittal anorectoplasty (PSARP) which will be limited to a smaller incision of 1–2 cm in the lower forms. This technique involves a posterior midline division of the structures up to the rectum. It has revolutionized the surgical approach by permitting a better exposition of the anatomy [32]. Cloaca and rectovesical fistula may require an abdominal approach that can be performed open or by laparoscopy [33]. Laparoscopically assisted anorectal pull-through (LAARPT) has gained popularity and offers the advantages of a good visualization of the rectal fistula and surrounding structures, accurate placement of the bowel through the anatomic midline and levator sling, and minimally invasive abdominal wound and perineal dissection [34].

Outcome

Modern surgical techniques and neonatal care have improved the outcomes of all the congenital malformations and ARM are not an exception. Mortality of patients with ARM had been between 10 and 20 % and has decreased to 3 % more recently. It is principally due to the severe associated anomalies. The mortality is about three times higher in patients with high anomalies than in patients with low anomalies [3].

Operative Complications

A colostomy is useful in higher forms to decompress the distal rectosigmoid and assess the anatomy preoperatively [28]. However, it carries a risk of morbidity. Prolapse and stricture

are the most common complications. Specific colostomy complications in ARM patients are related to the position of the colostomy: if too proximal, the rectum may not be well decompressed and megarectosigmoid predisposes to long-term constipation and overflow incontinence. On the other hand, a colostomy too distal needs to be replaced at the definitive repair to allow the rectum to reach the perineum.

Following pull-through, wound infection, dehiscence, and retraction with varying severity may occur. Deeper infection may lead to acquired rectal atresia and/or recurrent fistula requiring reoperation and leading to long-term functional sequelae [35]. Urologic injury is a well-known complication, especially in boys [36]. The risk is decreased with PSARP if an adequate preoperative colostogram is performed [37]. With the laparoscopic approach, the surrounding structures such as bladder, ureter, vas deferens, prostate, seminal vesicles, and urethra are visualized but still at risk for traumatism. Posterior urethral diverticula have more frequently been described in intermediate forms and after laparoscopic repair. Anal stenosis and rectal mucosal prolapse are commonly seen after pull-through. It is thought that postoperative anal stricture is prevented by an adequate anal dilatation program. Contrary to what was previously thought, there seems to be no significant difference in rates of mucosal prolapse between laparoscopic and open approaches [38].

Early Outcome in Childhood

Abnormal bowel function is common. After closure of the colostomy, patients with higher forms of ARM often develop frequent bowel movements causing perineal skin excoriations. This problem will continue to be particularly challenging on the long term if the terminal rectal reservoir has been resected. Constipation is a major problem affecting half of the patients with ARM and it is even more frequent in lower forms of ARM. It needs to be detected and treated aggressively in order to prevent the development of megarectum and pseudoincontinence [39, 40].

Evaluation of Long-Term Functional Outcome

In the literature, there is a great variation in the criteria used to evaluate long-term results after repair of ARM [41]. The multiple scoring methods based on subjective parameters that have been designed to quantify the bowel function have made comparisons among studies difficult [3, 42]. The Krickenbeck outcome classification tried to solve this problem (Table 29.4). This descriptive, nonscoring method is applicable after the age of 3 and permits a uniformization of the report of results [2]. It has been used in most recent publications [43–47].

Table 29.4 International classification (Krickenbeck) for postoperative results

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

From Holschneider A, Hutson J, Pena A, Beket E, Chatterjee S, Coran A, et al. Preliminary report on the International Conference for the Development of Standards for the Treatment of Anorectal Malformations. J Pediatr Surg. 2005;40(10):1521–6, with permission

Manometry has been the principal method to assess objectively the postoperative sphincter function. Correlation with clinical results is sometimes conflicting [3]. Clinical continence has been positively correlated with anal resting pressure [48–53], voluntary squeeze pressure [54], and rectal sensitivity assessed by balloon inflation [49, 54, 55]. The presence of the inhibitory rectoanal reflex is also described as a good prognostic factor [48–50, 56]. Colonic motility has also been studied. Hypomotility tended to be localized in the rectosigmoid in low ARM and was more generalized in high ARM [57]. Propagation of excessive numbers of high-amplitude propagating contractions (HAPC) into the neorectum may be a contributing factor to fecal incontinence in patients with repaired ARM [51].

Morphologic evaluation of the sphincter can be performed by echoendosonography [53, 55, 56] or magnetic resonance imaging (MRI) [58, 59]. Echoendosonography visualizes disruption or scar of the sphincters. MRI not only shows the sphincter complex, but it also allows the assessment of the placement of the bowel in relation to the sphincters and the anorectal angle. The predictability of the functional outcome with MRI is not clear [60].

Long-Term Outcome

According to Pena's extensive series of more than a 1000 of patients over two decades, 77 % of patients have voluntary bowel movements by the age of 3 [30]. Half of them soil their underwear occasionally, meaning that only 37.5 % are totally continent. Despite the fact that 25 % are totally incontinent, a definitive repair of all the types of ARM is still recommended because a bowel management program can be effective to treat the fecal incontinence and keep the patients

clean. It is however important to give realistic information to parents about what to expect in the long term since the outcome is related to the severity of the anomaly. Voluntary bowel movements are possible in 90 % of patients with rectal atresia/stenosis, perineal fistula, vestibular fistula, and imperforate anus without fistula. However, total continence is achieved in only half of the vestibular fistula and imperforate anus without fistula. Gender differences have also been noted with less incontinence and constipation in males than in females with perineal fistulas [45]. According to that study, perineal and vestibular fistulas had similar outcomes in girls. Regarding higher forms, voluntary bowel movements are present in 80 % of patients with a short cloaca or a bulbar rectourethral fistula, but only 30 % do not have fecal soiling. Prostatic rectourethral fistula and long cloaca have voluntary bowel movements in 73 and 55 % of cases, but only 45 and 39 % do not have fecal incontinence. Rectovesical fistula has the worst prognostic with 35 % on voluntary bowel movements and no patient without soiling [30].

With the advent of the LAARPT, it became crucial to study the outcome of this technique compared to PSARP. A prospective study of 24 cases of high-intermediate ARM found no differences in sphincter thickness as assessed by echoendosonography and MRI, but the clinical score was better for LAARPT [43]. A randomized control trial (RCT) did not find a difference in clinical outcomes in the short term, but the anal resting pressure assessed by manometry was improved [61]. A systematic review and meta-analysis grouping this RCT and six retrospective cohorts for a total of 187 patients found no difference in rates of defecation scores [38]. However, defecation outcomes were inconsistently reported and some reports included patients younger than 3 years old.

Long-Term Sequela Related to Associated Anomalies

Urinary incontinence from a *neurogenic bladder* is expected after repair of a cloaca but should be rare in male except if there is associated abnormal sacrum or spine [23, 25]. A third of patients with short cloaca require intermittent catheterization and long cloaca require intermittent catheterization in 70–80 % of cases [62]. Patients with cloaca are also at risk for chronic renal failure due to structural anomaly of the urinary tract such as renal dysplasia, ectopic/solitary/duplex kidney, and ureteropelvic junction obstruction. Vesicoureteral reflux and sacral abnormality are present in the majority of them [63].

Fertility does not seem to be affected in low forms of ARM [64], but it is decreased in higher forms [65]. Gynecological problems are usually related to the associated defects and have been discussed earlier. In males, erectile dysfunction, weak or missing erection, and retrograde ejaculations have been reported [65]. Avoidance of *sexual activity* may be chosen by patients because of poor bowel continence (20 of the patients with high anomalies and 13 % of the patients with low anomalies) [64, 65].

Methods to Improve Fecal Continence

Bowel Management Program

Because the fecal incontinence can have disastrous consequences on self-esteem and quality of life, it is ideal to establish a bowel management program before the entrance to school. This program consists of the daily administration of enema by the parents to clean the colon. Before starting it, it is important to understand the physiopathology of fecal incontinence: overflow pseudoincontinence and true fecal incontinence [66]. The differentiation between the two is essential because the treatment is different. Pseudoincontinence is caused by constipation and is suspected in the presence of a history of stool impaction (fecaloma on physical examination or on an abdominal X-ray, dilatation of the rectosigmoid on a barium enema). Colonic motility is decreased as can be demonstrated by colonic manometry or scintigraphy. True fecal incontinence is caused by increased motility, the absence of rectal reservoir, and sphincter failure. It is suspected in cases of diarrhea, when a barium enema shows a non-dilated colon with haustrations going down into the pelvis [30]. In the first group, the treatment consists of large-volume enemas with additives such as glycerin, bisacodyl, or phosphate administrated every night. The second group is easier to clean with smaller volume of saline enemas but will also require a constipating diet and medications to decrease bowel motility (e.g., loperamide) [28]. The bowel management program is generally well accepted by the children, but when they become adolescents, antegrade enema through an appendicostomy or a cecostomy constitute better solutions because they allow a self-administration of the colonic irrigation. Antegrade enemas have been shown to improve quality of life of patients [67].

Surgical Alternatives

In certain selected cases, resection of the dilated distal segment may be successful in treating constipation and fecal incontinence [68], but it can also convert a case of overflow incontinence to one of true incontinence because of the loss of the rectal reservoir. Optimal conservative management seems to have similar bowel functional outcome to the surgical treatment [69]. Redo surgery for mislocation of the rectum can be offered in patients with good prognostic factors, but it

does not necessarily lead to improved fecal continence [70, 71]. Different sphincter reconstructions have been proposed, but the long-term results are not convincing [3].

Other Alternatives

Sacral nerve stimulation (SNS) has shown promising results for children with urinary and fecal incontinence in a randomized crossover study [72]. Etiologies for incontinence were mainly of neurological origin. SNS consists of the surgical implantation of a neuromodulator in the S3 foramen. It is well tolerated by the patients. Other groups are collecting prospective data on that therapy [73]. *Biofeedback conditioning* has also been used to treat fecal incontinence with limited results. It is effective when the functional and morphologic assessment pretreatment is favorable [74]. It may represent an important adjunct to a multidisciplinary behavioral treatment [75, 76].

Conclusion

Despite significant improvements, the results of surgery are not optimal in a significant proportion of patients with ARM and these patients need careful follow-up. Children with ARM are at increased risk for behavioral and social problems. Since there are conflicting results about the correlation of those problems with the level of continence [77, 78], all patients should be followed by a multidisciplinary team including not only physicians but also nurses, psychologists, social workers, physiotherapists, and nutritionists [66]. The benefits of such multidisciplinary behavioral treatment strategy have been established [75, 76].

References

1. Brenner E. Congenital defects of the anus and rectum. Surg Gynecol Obstet. 1975;20:579–98.
2. Holschneider A, Hutson J, Pena A, Beket E, Chatterjee S, Coran A, et al. Preliminary report on the international conference for the development of standards for the treatment of anorectal malformations. J Pediatr Surg. 2005;40(10):1521–6.
3. Rintala RJ, Pakarinen MP. Imperforate anus: long- and short-term outcome. Semin Pediatr Surg. 2008;17(2):79–89.
4. Kluth D. Embryology of anorectal malformations. Semin Pediatr Surg. 2010;19(3):201–8.
5. Midrio P, Nogare CD, Di Gianantonio E, Clementi M. Are congenital anorectal malformations more frequent in newborns conceived with assisted reproductive techniques? Reprod Toxicol. 2006;22(4):576–7.
6. Castori M, Rinaldi R, Capocaccia P, Roggini M, Grammatico P. VACTERL association and maternal diabetes: a possible causal relationship? Birth Defects Res A Clin Mol Teratol. 2008; 82(3):169–72.
7. Frias JL, Frias JP, Frias PA, Martinez-Frias ML. Infrequently studied congenital anomalies as clues to the diagnosis of maternal diabetes mellitus. Am J Med Genet A. 2007;143A(24):2904–9.
8. Cuschieri A, Group EW. Anorectal anomalies associated with or as part of other anomalies. Am J Med Genet. 2002;110(2):122–30.
9. Mundt E, Bates MD. Genetics of Hirschsprung disease and anorectal malformations. Semin Pediatr Surg. 2010;19(2):107–17.
10. Levi AC, Borghi F, Garavoglia M. Development of the anal canal muscles. Dis Colon Rectum. 1991;34(3):262–6.
11. Bourdelat D, Barbet JP. Morphological differentiation of the anorectal sphincter in the human embryo and fetus. Chir Pediatr. 1990;31(1):12–7.
12. Lerone M, Bolino A, Martucciello G. The genetics of anorectal malformations: a complex matter. Semin Pediatr Surg. 1997; 6(4):170–9.
13. Teixeira OH, Malhotra K, Sellers J, Mercer S. Cardiovascular anomalies with imperforate anus. Arch Dis Child. 1983;58(9): 747–9.
14. Olgun H, Karacan M, Caner I, Oral A, Ceviz N. Congenital cardiac malformations in neonates with apparently isolated gastrointestinal malformations. Pediatr Int. 2009;51(2):260–2.
15. Tsakayannis DE, Shamberger RC. Association of imperforate anus with occult spinal dysraphism. J Pediatr Surg. 1995;30(7):1010–2.
16. Currarino G, Coln D, Votteler T. Triad of anorectal, sacral, and presacral anomalies. AJR Am J Roentgenol. 1981;137(2):395–8.
17. Pena A. Anorectal malformations. Semin Pediatr Surg. 1995;4(1):35–47.
18. Rivosecchi M, Lucchetti MC, Zaccara A, De Gennaro M, Fariello G. Spinal dysraphism detected by magnetic resonance imaging in patients with anorectal anomalies: incidence and clinical significance. J Pediatr Surg. 1995;30(3):488–90.
19. Golonka NR, Haga LJ, Keating RP, Eichelberger MR, Gilbert JC, Hartman GE, et al. Routine MRI evaluation of low imperforate anus reveals unexpected high incidence of tethered spinal cord. J Pediatr Surg. 2002;37(7):966–9; discussion 9.
20. Tuuha SE, Aziz D, Drake J, Wales P, Kim PCW. Is surgery necessary for asymptomatic tethered cord in anorectal malformation patients? J Pediatr Surg. 2004;39(5):773–7.
21. Levitt MA, Patel M, Rodriguez G, Gaylin DS, Pena A. The tethered spinal cord in patients with anorectal malformations. J Pediatr Surg. 1997;32(3):462–8.
22. Hoekstra WJ, Scholtmeijer RJ, Molenaar JC, Schreeve RH, Schroeder FH. Urogenital tract abnormalities associated with congenital anorectal anomalies. J Urol. 1983;130(5):962–3.
23. Boemers TM, de Jong TP, van Gool JD, Bax KM. Urologic problems in anorectal malformations. Part 2: functional urologic sequelae. J Pediatr Surg. 1996;31(5):634–7.
24. Cortes D, Thorup JM, Nielsen OH, Beck BL. Cryptorchidism in boys with imperforate anus. J Pediatr Surg. 1995;30(4):631–5.
25. Boemers TM, Beek FJ, van Gool JD, de Jong TP, Bax KM. Urologic problems in anorectal malformations. Part 1: urodynamic findings and significance of sacral anomalies. J Pediatr Surg. 1996; 31(3):407–10.
26. Breech L. Gynecologic concerns in patients with anorectal malformations. Semin Pediatr Surg. 2010;19(2):139–45.
27. Levitt MA, Bischoff A, Breech L, Pena A. Rectovestibular fistula—rarely recognized associated gynecologic anomalies. J Pediatr Surg. 2009;44(6):1261–7. Discussion 7.
28. Levitt AP. Pediatric surgery. In: Coran A, editor. Pediatric surgery, vol. 2. 7th ed. Philadelphia: Elsevier Saunders; 2012. p. 1289–131.
29. Haber HP, Seitz G, Warmann SW, Fuchs J. Transperineal sonography for determination of the type of imperforate anus. AJR Am J Roentgenol. 2007;189(6):1525–9.
30. Pena A, Hong A. Advances in the management of anorectal malformations. Am J Surg. 2000;180(5):370–6.

31. Gross GW, Wolfson PJ, Pena A. Augmented-pressure colostogram in imperforate anus with fistula. Pediatr Radiol. 1991;21(8):560–2.
32. Pena A, Devries PA. Posterior sagittal anorectoplasty: important technical considerations and new applications. J Pediatr Surg. 1982;17(6):796–811.
33. Bischoff A, Pena A, Levitt MA. Laparoscopic-assisted PSARP—the advantages of combining both techniques for the treatment of anorectal malformations with recto-bladderneck or high prostatic fistulas. J Pediatr Surg. 2013;48(2):367–71.
34. Georgeson KE, Inge TH, Albanese CT. Laparoscopically assisted anorectal pull-through for high imperforate anus—a new technique. J Pediatr Surg. 2000;35(6):927–30; discussion 30–1.
35. Pena A, Grasshoff S, Levitt M. Reoperations in anorectal malformations. J Pediatr Surg. 2007;42(2):318–25.
36. Misra D, Chana J, Drake DP, Kiely EM, Spitz L. Operative trauma to the genitourinary tract in the treatment of anorectal malformations: 15 years' experience. Urology. 1996;47(4):559–62.
37. Hong AR, Acua MF, Pea A, Chaves L, Rodriguez G. Urologic injuries associated with repair of anorectal malformations in male patients. J Pediatr Surg. 2002;37(3):339–44.
38. Shawyer AC, Livingston MH, Cook DJ, Braga LH. Laparoscopic versus open repair of recto-bladderneck and recto-prostatic anorectal malformations: a systematic review and meta-analysis. Pediatr Surg Int. 2015;31(1):17–30.
39. Levitt MA, Kant A, Pena A. The morbidity of constipation in patients with anorectal malformations. J Pediatr Surg. 2010; 45(6):1228–33.
40. Burjonrappa S, Youssef S, Lapierre S, Bensoussan A, Bouchard S. Megarectum after surgery for anorectal malformations. J Pediatr Surg. 2010;45(4):762–8.
41. Al-Hozaim O, Al-Maary J, AlQahtani A, Zamakhshary M. Laparoscopic-assisted anorectal pull-through for anorectal malformations: a systematic review and the need for standardization of outcome reporting. J Pediatr Surg. 2010;45(7):1500–4.
42. Ochi T, Okazaki T, Miyano G, Lane GJ, Yamataka A. A comparison of clinical protocols for assessing postoperative fecal continence in anorectal malformation. Pediatr Surg Int. 2012;28(1):1–4.
43. Ichijo C, Kaneyama K, Hayashi Y, Koga H, Okazaki T, Lane GJ, et al. Midterm postoperative clinicoradiologic analysis of surgery for high/intermediate-type imperforate anus: prospective comparative study between laparoscopy-assisted and posterior sagittal anorectoplasty. J Pediatr Surg. 2008;43(1):158–62; discussion 62–3.
44. Hassett S, Snell S, Hughes-Thomas A, Holmes K. 10-year outcome of children born with anorectal malformation, treated by posterior sagittal anorectoplasty, assessed according to the Krickenbeck classification. J Pediatr Surg. 2009;44(2):399–403.
45. Stenstrom P, Kockum CC, Emblem R, Arnbjornsson E, Bjornland K. Bowel symptoms in children with anorectal malformation—a follow-up with a gender and age perspective. J Pediatr Surg. 2014;49(7):1122–30.
46. Chan KW, Lee KH, Wong HY, Tsui SY, Wong YS, Pang KY, et al. Outcome of patients after single-stage repair of perineal fistula without colostomy according to the Krickenbeck classification. J Pediatr Surg. 2014;49(8):1237–41.
47. Qazi SH, Faruque AV, Mateen Khan MA, Saleem U. Functional outcome of anorectal malformations and associated anomalies in era of Krickenbeck classification. J Coll Physicians Surg Pak. 2016;26(3):204–7.
48. Iwai N, Hashimoto K, Goto Y, Majima S. Long-term results after surgical correction of anorectal malformations. Z Kinderchir. 1984;39(1):35–9.
49. Hedlund H, Pena A, Rodriguez G, Maza J. Long-term anorectal function in imperforate anus treated by a posterior sagittal anorectoplasty: manometric investigation. J Pediatr Surg. 1992; 27(7):906–9.
50. Rintala RJ, Lindahl H. Is normal bowel function possible after repair of intermediate and high anorectal malformations? J Pediatr Surg. 1995;30(3):491–4.
51. Heikenen JB, Werlin SL, Di Lorenzo C, et al. Colonic motility in children with repaired imperforate anus. Dig Dis Sci. 1999;44(7):1288–92.
52. Senel E, Demirbag S, Tiryaki T, Erdogan D, Cetinkursun S, Cakmak O. Postoperative anorectal manometric evaluation of patients with anorectal malformation. Pediatr Int. 2007;49(2):210–4.
53. Caldaro T, Romeo E, De Angelis P, Gambitta RA, Rea F, Torroni F, et al. Three-dimensional endoanal ultrasound and anorectal manometry in children with anorectal malformations: new discoveries. J Pediatr Surg. 2012;47(5):956–63.
54. Molander ML, Frenckner B. Anal sphincter function after surgery for high imperforate anus—a long term follow-up investigation. Z Kinderchir. 1985;40(2):91–6.
55. Wang Z, Hu L, Jin X, Li X, Xu L. Evaluation of postoperative anal functions using endoanal ultrasonography and anorectal manometry in children with congenital anorectal malformations. J Pediatr Surg. 2016;51(3):416–20.
56. Keshtgar AS, Athanasakos E, Clayden GS, Ward HC. Evaluation of outcome of anorectal anomaly in childhood: the role of anorectal manometry and endosonography. Pediatr Surg Int. 2008;24(8):885–92.
57. Rintala RJ, Marttinen E, Virkola K, Rasanen M, Baillie C, Lindahl H. Segmental colonic motility in patients with anorectal malformations. J Pediatr Surg. 1997;32(3):453–6.
58. Raman VS, Agarwala S, Bhatnagar V, Gupta AK. Correlation between functional outcomes and postoperative pelvic magnetic resonance imaging in children with anorectal malformation. J Indian Assoc Pediatr Surg. 2015;20(3):116–20.
59. Gangopadhyay AN, Pandey V, Gupta DK, Sharma SP, Kumar V, Verma A. Assessment and comparison of fecal continence in children following primary posterior sagittal anorectoplasty and abdominoperineal pull through for anorectal anomaly using clinical scoring and MRI. J Pediatr Surg. 2016;51(3):430–4.
60. Wong KK, Khong PL, Lin SC, Lam WW, Lan LC, Tam PK. Postoperative magnetic resonance evaluation of children after laparoscopic anorectoplasty for imperforate anus. Int J Colorectal Dis. 2005;20(1):33–7.
61. Yang J, Zhang W, Feng J, Guo X, Wang G, Weng Y, et al. Comparison of clinical outcomes and anorectal manometry in patients with congenital anorectal malformations treated with posterior sagittal anorectoplasty and laparoscopically assisted anorectal pull through. J Pediatr Surg. 2009;44(12):2380–3.
62. Levitt MA, Pena A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg. 2010;19(2):128–38.
63. Warne SA, Wilcox DT, Ledermann SE, et al. Renal outcome in patients with cloaca. J Urol. 2002;167:2548–51.
64. Rintala R, Mildh L, Lindahl H. Fecal continence and quality of life in adult patients with an operated low anorectal malformation. J Pediatr Surg. 1992;27(7):902–5.
65. Rintala R, Mildh L, Lindahl H. Fecal continence and quality of life for adult patients with an operated high or intermediate anorectal malformation. J Pediatr Surg. 1994;29(6):777–80.
66. Maerzheuser S, Schmidt D, Mau H, Winter S. Prospective evaluation of comorbidity and psychosocial need in children and adolescents with anorectal malformation. Part one: paediatric surgical evaluation and treatment of defecating disorder. Pediatr Surg Int. 2009;25(10):889–93.
67. Mattix KD, Novotny NM, Shelley AA, Rescorla FJ. Malone antegrade continence enema (MACE) for fecal incontinence in imperforate anus improves quality of life. Pediatr Surg Int. 2007;23(12):1175–7.
68. Pena A, el Behery M. Megasigmoid: a source of pseudoincontinence in children with repaired anorectal malformations. J Pediatr Surg. 1993;28(2):199–203.

69. Borg H, Bachelard M, Sillen U. Megarectosigmoid in children with anorectal malformations: long term outcome after surgical or conservative treatment. J Pediatr Surg. 2014;49(4):564–9.
70. Pena A. Posterior sagittal anorectoplasty as a secondary operation for the treatment of fecal incontinence. J Pediatr Surg. 1983;18(6):762–73.
71. Brain AJ, Kiely EM. Posterior sagittal anorectoplasty for reoperation in children with anorectal malformations. Br J Surg. 1989;76(1):57–9.
72. Haddad M, Besson R, Aubert D, Ravasse P, Lemelle J, El Ghoneimi A, et al. Sacral neuromodulation in children with urinary and fecal incontinence: a multicenter, open label, randomized, crossover study. J Urol. 2010;184(2):696–701.
73. Sulkowski JP, Nacion KM, Deans KJ, Minneci PC, Levitt MA, Mousa HM, et al. Sacral nerve stimulation: a promising therapy for fecal and urinary incontinence and constipation in children. J Pediatr Surg. 2015;50(10):1644–7.
74. Caruso AM, Catalano P, Li Voti G, Salerno S, Casuccio A, Di Pace MR, et al. Prognostic evaluation of biofeedback response in patients treated for anorectal malformation. J Pediatr Surg. 2015; 50(10):1648–52.
75. van Kuyk EM, Wissink-Essink M, Brugman-Boezeman AT, Oerlemans HM, Nijhuis-van der Sanden MW, Severijnen RS, et al. Multidisciplinary behavioral treatment of defecation problems: a controlled study in children with anorectal malformations. J Pediatr Surg. 2001;36(9):1350–6.
76. Schmiedeke E, Busch M, Stamatopoulos E, Lorenz C. Multidisciplinary behavioural treatment of fecal incontinence and constipation after correction of anorectal malformation. World J Pediatr. 2008;4(3):206–10.
77. Ludman L, Spitz L, Kiely EM. Social and emotional impact of faecal incontinence after surgery for anorectal abnormalities. Arch Dis Child. 1994;71(3):194–200.
78. Diseth TH, Emblem R. Somatic function, mental health, and psychosocial adjustment of adolescents with anorectal anomalies. J Pediatr Surg. 1996;31(5):638–43.