An update on surgical and non-surgical treatments for vaginal hypoplasia

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BACKGROUND: In women with vaginal hypoplasia, such as in Mayer–Rokitansky–Küster–Hauser syndrome (MRKH) and in Complete Androgen Insensitivity Syndrome (CAIS), surgical vaginoplasty and non-surgical self-dilation treatments are available to lengthen the vagina and facilitate sexual intercourse, but the best treatment remains controversial. Vaginal dilation has been recommended as a first-line treatment, because of its less invasive character and high success rate. However, the exploration of factors associated with compliance and long-term outcome is incomplete, including whether psychological counselling needs to be embedded in treatment to maximize efficacy. It is not known if failed vaginal dilation therapy jeopardizes further surgical success outcomes, especially because in a number of these procedures ongoing vaginal dilation is required. In addition, if surgery is needed, there is a lack of evidence to inform physicians regarding the optimum surgical technique to use. Also, it is unclear whether maintenance dilation therapy in case of sexual inactivity is crucial to ensure functional success.

METHODS: In view of this ongoing debate, we performed a search of all published literature (English language only) restricted to the management of vaginal hypoplasia in patients with MRKH or CAIS from 1898 to March 2013 using Pubmed, Cochrane Library and Web of Science. Of the 6700 articles initially identified, a total of 190 studies are analysed. More specifically, by establishing the risk/efficacy profile...
Introduction

It is apparent that the clinical management of congenital disorders of sex development (DSD)—in which anatomical, gonadal or chromosomal sex is atypical—has been in a state of great flux, debate and controversy during the last decade (Zucker, 2002; Hughes et al., 2006). Advances in medical knowledge and understanding of psychosexual development, as well as an increased emphasis on the rights and autonomy of the individual, have all contributed to discussion about the role and efficacy of medical intervention (Dreger, 1998; Preves, 1998; Carmichael and Alderson, 2004; Creighton, 2004; Liao, 2006a, b). Clinical practices developed to promote psychosexual wellbeing remain the subject of critical review (Dreger, 2006).

Differential diagnosis

Patients with DSD requiring vaginal reconstruction, because of vaginal hypoplasia or aplasia, typically present with primary amenorrhea in adolescence with an otherwise normal growth and development (Nakhal and Creighton, 2012). The most commonly involved condition is Müllerian agenesis or Mayer–Rokitansky–Küster–Hauser syndrome (MRKH), occurring in 1 in 4000–5000 females (Rall et al., 2010; Nakhal and Creighton, 2012). Women with MRKH have a XX karyotype and an absent or rudimentary uterus and cervix and a short vagina resulting from failed embryonic development of the Müllerian duct (Nakhal and Creighton, 2012). The syndrome (i.e. vaginal hypoplasia) may be isolated (typical form, type I) but it is more frequently associated with malformations of the ovaries and/or renal system (atypical form, type II) and to a lesser extent systemic defects [Malformations Urinary, Cardiac and Skeletal (MURCS), Type III] (Oppelt et al., 2006). In familial cases, the syndrome appears to be transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity, which suggests the involvement of either mutations in a major developmental gene or a limited chromosomal imbalance. However, the aetiology of MRKH still remains unclear (Morcel et al., 2007).

The differential diagnosis of MRKH mainly includes 46,XY DSD, specifically androgen insensitivity syndrome in which the lack of a functional androgen receptor results in phenotypically normal female external genitalia (Quigley et al., 1995). These women have testes, absent Müllerian structures and a blind short vaginal pouch due to the action of anti-Müllerian hormone (Sarpel et al., 2005; Hurme et al., 2009). Estimated incidences vary according to the population studied, ranging from 1 in 41 000–120 000 (Quigley et al., 1995; Minto, 2004). In addition, vaginal hypoplasia can be associated with disorders of testosterone biosynthesis or other rare complex conditions affecting the urinary and gastrointestinal tracts, such as cloacal and anorectal anomalies (Michal et al., 2007). In pubertal females, differential diagnosis can be made by assessing serum testosterone levels and karyotype analysis. Conventional transabdominal, transinguinal or transrectal ultrasonography, 3D ultrasonography and magnetic resonance imaging can be used to evaluate the absence of the uterus and vagina and can in individual cases be helpful in definitively characterizing (reproductive) anatomy (American College of Obstetricians and Gynecologists (ACOG), 2013; Hall-Craggs et al., 2013; Grimbizis et al., 2013).

Compromised womanhood

Besides correct diagnosis of the underlying condition and evaluation for associated congenital anomalies, an important step in the effective medical management is psychosocial counselling before any treatment or intervention (ACOG, 2013). These conditions have devastating implications for fertility and sexual intercourse and affected women may experience variable levels of distress, connected to the perception of having a compromised womanhood and characterized by the fear of being devalued by others (Hecker and McGuire, 1977; Alderson et al., 2004). Sensitive pacing of information is recommended in order to allow young women and their family to make informed decisions about
different treatment modes and a realistic adaptation to living with this condition (ACOG, 2013).

Reproductive challenges

The adoption route has long been the sole option of family choice in women with these conditions. With the advent of IVF 20 years ago, assisted reproduction technology (ART) and gestational carriers have also provided fertility options in women with an ovarian reserve, such as in cases of MRKH (Edmonds, 2013). The frequent ectopic position of ovaries in these women (40%) is important to take into account for egg harvesting, as they may not be amenable to transvaginal collection (Hall-Craggs et al., 2013). A number of small series have reported clinical pregnancy rates of 17–37% (Petrozza et al., 1997; Beski et al., 2000; Brinsden, 2002; Raziel et al., 2012), with similar rates in women with type I and II MRKH, although the former needed fewer ampoules of gonadotrophin for stimulation and had a higher number of follicles, oocytes and cleaving embryos (Raziel et al., 2012).

Although many females with MRKH have complete aplasia of all Müllerian structures (Class U5/C4/V4 ESHRE/ESGE Classification; Grimbizis et al., 2013), 47–84% have uterine remnants, either bi- or unilateral rudimentary horns with cavity (Class U5a), or uterine remnants without cavity (Class U5b; Oppelt et al., 2012; Grimbizis et al., 2013). The presence of a horn with cavity containing functional endometrium (2–7%) is clinically important, because it is combined with cyclic pain and/or haematoc–cavity, necessitating treatment (ACOG, 2013). Conservative surgical management remains controversial and the possibility of conception after such an operation poses a unique therapeutic challenge (Deffarges et al., 2001). Total laparoscopic resection of the uterine remnants is typically recommended, but successful pregnancies have been achieved by uterine and cervical reconstruction, creation of a neovagina and placement of an urogenital conduit (or vaginal–uterine fistula tract; Hampton et al., 1990; Thijsen et al., 1990; Deffarges et al., 2001; Grimbizis et al., 2004; Doyle and Lafer, 2009). Although the overall success rate of these reconstructive procedures is 60% (Grimbizis et al., 2004), they are frequently complicated by fibrotic stenosis, recurrent obstruction and sepsis (Rook et al., 1995; Casey and Lafer, 1997), making hysterectomy, as well as the use of ART and a gestational carrier currently a safer option.

As most women without functional uteri still feel very strongly about being pregnant (Edmonds, 2013) and encouraged by the results of uterine auto- and allotransplantation and experiments resulting from offspring from a transplanted uterus in animals (Ramirez et al., 2011; Wran ning et al., 2011), the role of human uterine transplantation has been further investigated in the last decade (Brännström, 2013). Since the first unsuccessful attempt in 2000 (Fageeh Cools et al., 2006; Kaprova-Pleskacova et al., 2013). The need for the use of immunosuppressive agents and their teratogenic potential for fetal growth remains a major issue, and has an ethical dimension as the risk–benefit ratio in this type of surgery is different from life-saving forms of organ transplantation (Brosens et al., 2013; Caplan, 2013). Until further successful developments in the field, the discussion on ART and gestational carriers is appropriate and should allow these young women with MRKH to understand their limited reproductive potential for becoming a biological parent and may help them further deal with the diagnosis and its implications.

In women with 46,XY karyotypes, gonadal management requires additional attention, with the approach varying depending on the underlying DSD and its manifestation. As a general rule, Y chromosome bearing mal-developed gonads that remain within the abdomen will function poorly from a reproductive standpoint and are at high risk for malignancy (Cools et al., 2006). In women with complete androgen insensitivity syndrome (CAIS), retention of gonads through puberty is acceptable in terms of tumour risk, thus spontaneous puberty can be experienced. Although the risk of malignancy in CAIS, especially at an adult age, is not precisely known, it is significantly lower than in cases with dysgenetic gonads (Cools et al., 2006, 2011). Recent reports challenge the need to perform gonadectomy in CAIS women at all, since there have been anecdotal reports of loss of libido following gonadectomy, concerns about long-term hormonal replacement and even the potential of the gonads harbouring viable germ cells that could be used for procreation with future advanced technology (Deans et al., 2012). However, as a rule, a (near-)complete germ cell loss has been observed in adult CAIS gonads (Cools et al., 2005; Kaprova-Pleskacova et al., 2013). In addition, optimal modalities of surveillance and screening intervals for gonadal tumours remain to be defined (Cools et al., 2014).

Plethora of vaginal reconstruction methods

Sexually experienced patients may present with natural dilation of the vaginal dimple and occasionally require no additional treatment. Enlargement procedures for vaginal hypoplasia in non-sexually experienced women include surgical vaginoplasty and non-surgical dilation therapy (Deans et al., 2010). Tables I and II, and Fig. 1 provide an overview of the variety of techniques and their main advantages and disadvantages (based on Ismail et al., 2006; Michala et al., 2007; Schober, 2007; Thomas and Brock, 2007; Gargollo et al., 2009; Deans et al., 2010; Ozkan et al., 2011).

Vaginoplasty techniques

Dupuytren (1817, see Dupuytren, 1835) and later Amussat (Amussat, 1835) are frequently mentioned as being the first proponents of surgical correction, which involved creating a perineal pouch between bladder and rectum with strong digital pressure and then packing the cavity with linen (Minto and Creighton, 2003). Wharton (1938) and Counsellor (1948) subsequently refined this technique by using a mould covered with a rubber sheath to hold the perineal pouch open, which allowed spontaneous epithelialization to take place (Wharton, 1938; Counsellor, 1948). It became quickly clear that the mould had to be used for several hours every day to reduce vaginal strictures due to scar formation. Permanent dilation to prevent stenosis of the neovagina (3–6 months or longer) was further insisted upon by Banister and McIndoe (1938). They popularized a technique, first pioneered by Abbe (1898), in which split-thickness skin grafts taken from the anterior surface of the thigh or buttock were inserted over the mould, after dissection of a space between rectum and bladder (Abbe, 1898; McIndoe, 1950). There were problems with fistula formation secondary to the use of the mould and the need for lubrication as the skin graft tended to be rather dry (MacDougall and Creighton, 2004). Numerous modifications of the mould
material (soft, semi-rigid or rigid) or shape, and improvements in post-operative care have been suggested to reduce the incidence of complications (Golditch, 1968; Ulfelder, 1968; Khanna and Khanna, 1982). However, marked scarring at the donor site and vaginal stenosis or contracture, particularly at its distal end, remains a problem.

The problem of contraction of the vagina post-operatively was thought to be avoided with skin flap vaginoplasty and the use of full-thickness skin grafts from labia minora or thighs, first described by Graves in 1921, with disappointing results (Graves, 1921; Frank and Geist, 1927; Falls, 1940; MacDougall and Creighton, 2004). The technique was modified by Bhonsale and Sheares who lined the posterior wall of the rectovesical cavity with a single skin flap dissected from the vaginal dimple, retaining its attachment (Fortunoff, 1964). Fortunoff utilized a U-shaped skin flap and flap vaginoplasty (Fortunoff et al., 1964). Other skin flaps used included rotated buttock flaps (Hendren and Donahoe, 1980), and myocutaneous flaps, involving the gracilis muscle, a vulvobulbocavernous myocutaneous graft (Hatch, 1984) and rectus abdominis muscle, which also have been used with success in vaginal deficiencies following neoplasms or traumas (McCracken et al., 1976; Tobin and Day, 1988). Peduncled thigh flaps (Wee and Joseph, 1989), free flap graft from the scapula (Johnson et al., 1991; Hockel, 2003) and vulvoperineal fasciocutaneous flaps (Giraldo et al., 1996) have been used as well. Williams preferred vulvavaginoplasty, where an external pouch is created by suturing the labia majora to form a short vertical ‘vagina’, which can despite its unnatural axis be further expanded through dilator use or intercourse (Williams, 1964). Most of these techniques can suffer from visible scars and keloid formation, and lack of vaginal lubrication and hair regrowth in the neovagina, which can become stenosed (Ismail et al., 2006). In addition, a risk of squamous cell carcinoma has been reported (Creighton, 2004).

In an attempt to overcome some of the disadvantages of the skin graft techniques, a variety of other tissues have been used to line new vaginas. In 1934, Brindeau described a novel approach using chemically processed and sterilized freeze-dried human amniotic membranes that are considered immunologically inert and thus have low risk of graft rejection (Brindeau, 1934). It has the advantage that no graft site is required, thereby leaving no external scars for the patient to have to tolerate. However, it is important that the use of this material is properly governed and that donors are suitably screened for transmittable diseases (Ashworth et al., 1986). Various other authors have reported on the use of artificial or biological materials, including buccal mucosa (Lin et al., 2003), artificial dermis (atelocollagen sponge) and with use of basic fibroblast growth factor to accelerate epithelization (Noguchi et al., 2004), oxidized cellulose (Sharma et al., 2007), and autologous in vitro-cultured vaginal tissue (Panici et al., 2007). Pedunculated

## Table I Vaginal reconstruction methods.

<table>
<thead>
<tr>
<th>Non-surgical</th>
<th>Surgical</th>
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<tbody>
<tr>
<td>1. Simple pressure (Frank, 1938)</td>
<td>1. Surgical creation of a neovaginal space between bladder and rectum</td>
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<tr>
<td>2. Pressure from a bicycle stool (Ingram, 1981)</td>
<td>1.1 Simple reconstruction with insertion of form, without grafting (Wharton, 1938; Counsellor, 1948)</td>
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<td>3. Regular coitus (Serment et al., 1976; Tobin and Day, 1988)</td>
<td>1.2 Simple reconstruction with insertion of inlay graft over form</td>
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<td></td>
<td>(a) Split-thickness skin graft (Abbe, 1898; Banister and McIndoe, 1938)</td>
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<td></td>
<td>(b) Full-thickness skin graft and flap vaginoplasty</td>
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<td></td>
<td>Simple labia minora and thigh flaps (Graves, 1921)</td>
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<td></td>
<td>Tubed pedicle flap from thigh (Frank and Geist, 1927)</td>
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<td></td>
<td>Pedicled bladder flap (Krzeksi and Borkowski, 1983)</td>
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<td></td>
<td>Gracilis myocutaneous flaps (McCracken et al., 1976) and transpelvic rectus abdominis myocutaneous flaps (Tobin and Day, 1988):</td>
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<td></td>
<td>• Perineal artery axial flap of Hagerty (Hagerty et al., 1988)</td>
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<td></td>
<td>• Pudendal thigh flap vaginoplasty (Singapore flap; Wee and Joseph, 1989; Woods et al., 1992)</td>
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<td></td>
<td>• Free flap graft from scapula (Johnson et al., 1991)</td>
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<td></td>
<td>• Vulvoperineal fasciocutaneous flap (the Malaga flap; Giraldo et al., 1996)</td>
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<td></td>
<td>(c) Allogenic tissue: Amnion (Brindeau, 1934), epidermal sheets (Carranza-Lira et al., 1999)</td>
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<td>(d) Peritoneum (Davydov, 1969; Rothman, 1972)</td>
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<td></td>
<td>(e) Artificial grafts: Interceed adhesion barriers (Jackson and Rosenblatt, 1994), silicone membrane with incorporation of recombinant fibroblast growth factor (Noguchi et al., 2004)</td>
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<td>(f) Tissue expanders (Liford et al., 1988)</td>
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<td></td>
<td>(g) Autologous in vitro-cultured vaginal tissue (Panici et al., 2007), autologous buccal mucosa (Lin et al., 2003)</td>
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<tr>
<td>2. Bowel vaginoplasty</td>
<td>2.1 Ileum (Baldwin, 1904), sigmoid colon (Ruge, 1914) or caecum and ascending colon (Kun, 1972)</td>
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<td></td>
<td>2.2 Rectum (Popoff, 1910)</td>
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<td></td>
<td>2.3 Free jejunal autograft (Emiroglu et al., 1999)</td>
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<td>3. Vulvavaginoplasty (Williams, 1964)</td>
<td>4. Surgical traction</td>
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<td></td>
<td>4.1 Vecchietti procedure (Vecchietti, 1965)</td>
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<td>4.2 Balloon vaginoplasty (El Saman et al., 2007; Darwish, 2010)</td>
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<p>| Surgical traction | (a) Split-thickness skin graft (Abbe, 1898; Banister and McIndoe, 1938) |
| | (b) Full-thickness skin graft and flap vaginoplasty |
| | Simple labia minora and thigh flaps (Graves, 1921) |
| | Tubed pedicle flap from thigh (Frank and Geist, 1927) |
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<table>
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<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
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| **1. Dilation method (Frank/Ingram)** | Non-invasive  
No hospitalization  
Psychological advantage of the subject being in control  
Preserves vaginal tissue  
Cost-effective, inexpensive  
Minimal morbidity and complications  
After failed treatment, the option still exists to proceed to surgical neovaginal creation | Motivated and mature patients required (low compliance)  
Time-consuming  
Discomfort and constant reminder of difference  
Awkward sitting on an Ingram stool  
Manual fatigue, boring and inability to create enough perineal pressure (Frank)  
Limited success in younger patients (< 18 years)  
Long-term dilation needed  
Poor results with skin dimple  
Increased risk of vaginal prolapse |
| **2. Vecchietti procedure** | Preserves vaginal tissue  
Laparoscopic approach minimally invasive  
No excessive mucus production or vaginal stenosis | Pain and therefore need for strong analgesia during daily tightening  
Post-operative self-dilation required  
Significant potential complications because of the limited retrovesicorectal space into which the traction threads need to be placed  
Pliable tissue required (not recommended in the presence of scars from previous reconstructive surgeries)  
Increased risk of vaginal prolapse |
| **3. Intestinal vaginoplasty (sigmoid colon, ileum, jejunum)** | Lubricated segment with reliable blood supply  
Grows with the patient (advantageous for younger children)  
No scarring  
No dilation needed  
Low rate of stricture  
Can be performed with previous extensive surgery | Requires laparotomy and bowel anastomosis  
Prolapse 3–8%  
Excessive discharge  
Complication rate of 16–26% (post-operative ileus, bowel obstruction, diversion, ulcerative colitis, adenocarcinoma) |
| **4. Davydov procedure (peritoneum)** | Suitable for women who had previous pelvic surgery  
Lack of granulation tissue  
No scar formation | Decreased lubrication  
Potential for bladder and rectum injury  
Potential infections and prolapse  
Post-operative dilation needed |
| **5. McIndoe procedure (split-thickness skin grafts)** | Vaginal approach avoids laparotomy  
No bowel anastomosis  
High rate of graft take  
Low rate of prolapse | Post-operative dilation needed  
High rate of graft contracture and neovaginal stenosis  
Disfiguring scar at the donor site  
Potential of graft infection  
Lack of lubrication  
Risk for squamous cell carcinoma  
Complication rate up to 14% |
| **McIndoe (modified)**  
Allogenic tissue  
Autologous vaginal mucosa | Reduction of the occurrence of chronic granulation tissue  
No donor site scarring  
No stenosis  
No vaginal dryness | Risk of allograft rejection  
Risk of transmission of infectious diseases  
Morbidity connected with the removal of the mucosa  
Long time needed for the meshed vagina to colonize the entire neovagina |
| **6. Full-thickness skin grafts**  
Myocutaneous/fasciocutaneous flaps  
Pudendal thigh flap  
Labia minora flaps  
Malaga flap  
Singapore flap  
Scapula flap | Good pelvic support following exenteration  
Can be done at time of exenteration  
Good blood supply, low infection rate  
Flap incision incorporated into laparotomy site  
Pedicled tissue form better than free-tissue, because no dilation required  
No skin graft with pudendal thigh flaps | High rate of prolapse and flap loss ( gracilis)  
Skin appendages  
Deficient lubrication  
Disfiguring scar at the donor site  
Wound site infection  
Hair regrowth in the neovagina |
| **7. Williams Vulvavaginoplasty (flaps from labia majora)** | Simple surgery  
Non-invasive | Hair bearing skin  
Sexual contact is difficult due to angle of the external vagina  
Insufficient vaginal depth, no feeling of penetration  
Wound opening, haematoma, trauma infection |
bladder wall flap (Krzeski and Borkowski, 1983) and peritoneum from the Douglas pouch (i.e. Davydov procedure) have been used in a combined abdominoperineal approach (Davydov, 1969; Rothman, 1972). Davydov developed a three-stage operation involving dissection of the rectovesical space with abdominal mobilization of the peritoneum, attachment of the peritoneum to the created introitus and finally closure of the neovaginal vault with purse-string suture (Davydov, 1969; Davydov and Zhvitiashvili, 1974; Ward et al., 1998). The claimed advantage of this technique by the authors is the lack of granulation and scar formation. The procedure was modified to a laparoscopic

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**Figure 1** Vaginal reconstruction techniques. Different vaginal reconstruction techniques. (A) Vecchietti technique: pressure is applied on the vaginal dimple by an acrylic olive connected by threads that pass through the potential neovaginal space, are guided preperitoneally along the abdominal wall and exit via the anterior abdominal wall where they are connected to a traction device. The threads are tightened daily. (B) Williams’ procedure: the Labia majora are used to line an external pouch formed by a U-shaped perineal incision. (C) Bowel vaginoplasty: a short segment of bowel (ileum or sigmoid colon) is isolated. The mesentery of the bowel segment is extensively dissected upwards in order to connect this neovagina with minimal tension. (D) Mclndoe procedure: split-thickness skin grafts are obtained from the thighs or buttocks and adapted around a mould to line the dissected space between rectum and bladder. (E) Davydov procedure: A transverse incision is made below the urethra; peritoneum is dissected off the rectum, bladder and side wall of the pelvis using fingers, and developing a space; the canal is tightly packed and an incision is made in the peritoneum over the pack; stay sutures in the peritoneum are used to pull a tube of peritoneum towards the perineum; the edges of the peritoneal tube are sutured to the skin of the introitus and the abdominal end of the tube is closed. (F) Vaginal dilation techniques: Frank vaginal dilators of different sizes increasing in length and width, and the Ingram stool method whereby patients are instructed to sit on bicycle seat-shaped stool for short periods with a vaginal dilator held in position in or at the vaginal opening to stretch the vaginal tissue.
approach, having the advantages of less bleeding and post-operative pain in addition to shorter hospital stay, faster recovery and better cosmetic outcome (Soong et al., 1996). These merits are specifically important in adolescent patients in whom cosmesis may be very important and a faster recovery would allow for earlier return to school (Pandis et al., 2009).

The use of bowel segments, reported as early as 1892 by Sneguireff, has gained enormous popularity for vaginal reconstruction in DSD and is also widely used following pelvic exenteration for cancer (Minto and Creighton, 2003). Because of the high morbidity and mortality rates when ileum segments were first used by Baldwin in 1904, the technique was largely abandoned until 1961, when the use of a sigmoid loop was described (Baldwin, 1904; Popoff, 1910) and later the use of cecum and jejunum (Kun, 1972; Emiroglu et al., 1996). A laparoscopic approach has been carried out since 1996 (Ohashi et al., 1996), but the procedure is still most frequently performed through a laparotomy. Overall, the main advantages of this operation are said to be the lack of shrinkage—with no long-term vaginal dilation needed—and the natural lubrication provided by the mucous production that obviates the need for artificial lubricants and decreases the risk of dyspareunia (Gatti et al., 2010). Greatest concerns surrounding this operation are bleeding or copious and smelly vaginal discharge, which also may mask adenocarcinoma (Creighton, 2004; Davies et al., 2005). Diversion colitis may also occur, possibly due to a lack of short-chain fatty acids normally present in colonic contents and required for mucosal integrity, but is less of a problem with ileum than with colon segments (Minto and Creighton, 2003).

Finally, other surgical techniques are based on passive traction rather than dilation. In 1965, Vecchietti proposed a device permitting an upwards traction on the retrohymenal fovea by an acrylic olive and the creation of a neovaginal space in 1 week, this without the use of extraneous tissue (Vecchietti, 1965, 1979). The laparoscopic adaptation proposed in 1992 offers enhanced speed and ease (Gauwerky et al., 1992). The complication rate including bladder and rectal wall injury is reported to be low (Fedele et al., 2008b). However, a more common drawback for this procedure is the pain resulting from the sustained traction which necessitates a hospital stay throughout the whole traction process (Deans et al., 2010). Balloon vaginoplasty is based on the same principle, however, traction and dilation of the vaginal dimple is exerted by a Foley catheter with an inflated balloon (El Saman et al., 2007; Darwish, 2010). The authors claim that the main advantage of this technique is the neovaginal width, which can be manipulated according to balloon distension.

**Vaginal dilation techniques**

Because there is pliable perineal skin between the urethra and anus in women with vaginal hypoplasia, coitus has been shown to lead to an increase in vaginal depth and width (Masters and Johnson, 1966; Serment et al., 1969; D’Alberton and Santi, 1972; Moen, 2000). In young women with an understanding and cooperative partner, excellent results can be obtained with little intervention from medical professionals (Lappohm, 1995). When women do not have a partner or vaginal depth does not increase by coital dilation, supportive treatment with dilators has been proposed.

Frank described in 1938 the use of Pyrex tubes of gradually increasing sizes (0.8, 1.5 and 2.0 cm in diameter) to force the mucous membrane inward into the introital region (Frank, 1938; Lee, 2006). Interestingly, for almost 40 years this technique was only infrequently used, although his series and the majority of case reports suggested that this approach was one of promise (Holmes and Williams, 1940; Steinmetz, 1940; Campbell, 1941; Marshall, 1944; TeLinde, 1946; Williams, 1957). In 1981, Ingram modified the technique based on presumed inconveniences of Frank’s method, such as sheer fatigue of the hands and fingers, the need to squat, and the inability to perform other productive activities during the procedure. He inserted dilators into the saddle of a bicycle stool and had the patients sit astride this to gently create perineal pressure (Ingram, 1981). The seat was later modified by Lee (2006) and Lankford and Haefner (2008).

**To dilate or not to dilate?**

Non-surgical vaginal dilation has been put forward by ACOG in 2002 as a first choice treatment, because it is a patient-driven technique that is easy to perform, cost–effective and safe (Gargollo et al., 2009; Routh et al., 2010; ACOG, 2013). Meanwhile, the concept of surgery for DSD conditions became increasingly controversial and led to a call in some quarters for a moratorium on genital surgery as long as long-term data are unavailable (Schober, 1998; Creighton, 2004). Successful neovaginal creation by dilation obviates the need for major surgery in most patients, while those not achieving adequate vaginal length with dilation can still undergo vaginoplasty as a second-line intervention. It is expected that only 85% of women will achieve a functional vagina without a surgical approach (Edmonds, 2000). Reasons for failure, however, need further clarification. Moreover, it is not known if failed vaginal dilation therapy jeopardizes further surgical success outcomes, especially because in a number of these procedures ongoing vaginal dilation is required. In addition, if surgery is needed, there is a lack of evidence to inform physicians regarding the optimum surgical technique to use. Also, the extent to which psychological interventions are needed to maximize treatment success needs to be further elucidated. In view of this ongoing debate and in order to provide a comprehensive, non-biased reference tool, the available literature on the various approaches to vaginal reconstruction is reviewed below. The anatomical outcomes, referring to vaginal capacity, and functional outcomes, referring to sexual activity levels and successful coital or non-coital sexual activities, of the current techniques reported hitherto are discussed.

**Methods: outcome studies under scrutiny**

A search of all published literature restricted to the management of vaginal hypoplasia in patients with MRKH or CAIS since 1898 up to March 2013 was conducted using Pubmed, Cochrane Library, Web of Science, as well as hand searches for relevant articles not initially identified using the search parameters (MRKH, CAIS, vaginal agenesis, vaginal hypoplasia/aplasia plus vaginoplasty, vaginal dilation, (non-)surgical management, neovagina, vaginal reconstruction). Studies were restricted to systematic reviews, RCTs, controlled clinical trials and observational studies that provided data on surgical or non-surgical indications, anatomical success, intraoperative and short- and long-term complications, and long-term sexual function and wellbeing if available. Single case reports, non-English manuscripts, and manuscripts solely on patients born with ambiguous genitalia (e.g. congenital adrenal hyperplasia) or...
associated urogenital (including lower urinary or anorectal) anomalies were excluded.

Approximately 6700 articles were identified, of which 190 articles were included. The studies were carried out across all continents. In the majority of the studies, no information was provided on the indication for the particular treatment offered, there was no blinding of either the patients or the clinicians, with only one study having randomized care (Cao et al., 2012). Because of the diverse range of details available with mixed information and follow-up, the use of the recommended methodology from the preferred reporting items from systematic reviews and meta-analyses (PRISMA) checklist for meta-analyses was unfortunately not possible (Moher et al., 2009). We nevertheless attempted to synthesize and dichotomize data for analysis using statistical software. When different vaginal reconstruction regimens were separately discussed in the studies included, the results were separately handled (Supplementary data. Tables I–III, references 13, 23, 33, 35, 41, 42, 44, 46, 49, 102, 108, 126, 164, 171, 194, 202, 204, 227, 268, 287, 311, 312, 328). For analysis purposes, the surgical options were divided into seven major types: (i) vaginoplasty without grafting (i.e. Wharton procedure) (11, 41, 46, 51, 111, 202, 206, 279, 286, 314, 319); (ii) McIndoe procedures (7, 11, 27, 35, 38, 41, 46, 60, 72, 97, 98, 102, 108, 120, 121, 135, 164, 171, 173, 174, 179, 186, 204, 211, 216, 243, 244, 249, 259, 268, 275, 283, 287, 291, 297, 300, 320, 327, 328); and modified procedures (ammonium (10, 24, 82, 114, 126, 171, 229, 235, 277), absorbable adhesion barrier (85, 163, 230, 285) and buccal mucosa (196, 334, 335)); (iii) skin flap procedures, including myocutaneous/fasciocutaneous flaps (130), pudendal thigh flaps (3, 225), full-thickness skin grafts from groins/buttock (4, 101, 295), labia minora flaps (22, 110, 158, 254, 256, 308) or a mix of skin flap techniques (304); (iv) Vulvavaginoplasty (i.e. Williams procedure) (46, 64, 108, 164, 239, 323, 324); (v) peritoneal vaginoplasty (i.e. Davydov procedure) carried out laparatomically (75, 76, 222, 294, 315) or laparoscopically (8, 23, 44, 70, 107, 129, 137, 197, 200, 289, 336); (vi) bowel vaginoplasty with use of sigmoid colon, cecum or ileum (14, 35, 36, 39, 41, 44, 46, 49, 53, 69, 81, 92, 109, 118, 119, 127, 132, 134 147, 148, 149, 159, 170, 176, 179, 203, 207, 237, 238, 240, 249, 257, 260, 263, 292, 302, 305, 307, 318, 332, 333, 335), jejunum (245, 274) or rectosigmoid (84, 188, 231); and (vii) Traction vaginoplasty, consisting of the Vecchietti technique (23, 26, 33, 34, 66, 104, 105, 112, 125, 128, 166, 172, 175, 183, 311, 312) or balloon traction (71, 93, 94). Five studies reported the outcomes of different vaginoplasty procedures combined (13, 42, 194, 227, 309). Seventeen studies also specifically mentioned the sexual long-term outcomes in women without treatment (with or without coitus) (42, 68, 185, 194, 223, 257, 284, 328) or after mixed treatment regimens (dilation, surgery, coitus or no treatment) (54, 143, 168, 177, 185, 220, 228, 326). Lastly, vaginal dilation studies are reviewed (5, 13, 30, 42, 46, 49, 59, 91, 102, 116, 122, 160, 161, 164, 185, 194, 202, 204, 215, 221, 227, 233, 265, 266, 268, 287, 311, 313, 325, 329) (Fig. 2).

To assess diagnosis-related success rates, we included in a separate analysis only studies in which the diagnosis of the participants was specified as either 46,XX MRKH (n = 151 studies) or 46,XY disorders of testosterone biosynthesis or action (mainly CAIS) (n = 22 studies) (10, 12, 42, 59, 93, 94, 102, 118, 121, 125, 127, 161, 173, 199, 220, 222, 229, 257, 309, 326, 328, 329), including nine studies in which there was a mix of 46,XX and 46,XY, but differences between the two groups of women were separately discussed (10, 121, 125, 127, 161, 173, 199, 223, 229). Tables III–VI summarize the outcomes of the various surgical and non-surgical procedures and influencing factors regarding anatomical and functional success, clarified for each of the studies.

**Practice informing theory**

Establishing the risk/efficacy profile of the different surgical and non-surgical techniques, we evaluate if vaginal dilation, proposed as first-line technique is justified on an evidence base.

**Comprehensive synopsis of main outcomes**

**Anatomical success and complications**

Anatomical success, referring to an adequately sized vagina, seems to be in most studies defined on the basis of two (related) parameters. The first is vaginal length, agreed upon to be at least 6 cm. The second is an absence of complications (and in particular contractures affecting vaginal length, or scar formation), considered to be associated with a cosmetically pleasing result (in the rule according to the clinician’s perspective). Reference values for normal vaginal length were previously described to be 7–13 cm (mean 9.25 ± 1.56 cm; Lloyd et al., 2005). Non-surgical vaginal dilation treatment has been shown to normalize vaginal length in at least 75% of women, irrespective of karyotype or underlying diagnosis. However, when anatomical success was defined as a length of ≥7 cm, all vaginoplasty techniques yielded significantly higher anatomical success rates (>90 versus 78% after vaginal dilation).

In contrast, intratreatment complication rates (i.e. rectal, urethral or bladder injuries, haemorrhage), as well as short- and long-term post-operative complication rates [in the short-term: Infection (including urinary tract infection), haematoma, anastomotic leak; in the long-term prolapse, stenosis, stricture or contracture, scarring, vaginal discharge, bowel obstruction, granulation tissue, hair regrowth, rectovaginal or vesicovaginal fistulae, graft necrosis] were significantly lower within the vaginal dilation series when compared with the published surgical series. Main complications in the vaginal dilation group were urinary complaints and infrequent pain and bleeding (≤1%). Similar complications and rates were found with use of traction vaginoplasty techniques, with the exception of intraoperative bladder trauma (2%) being more surgery-prone. Complications of the majority of surgical techniques involving a dissection between the rectum and bladder were intraoperative rectal or bladder perforation (1–4%) and short- and long-term urinary tract infections (4–7%), vaginal strictures, contractures or stenosis (4–9%), and vesicovaginal or rectovaginal fistulae (1–3%). In the case of skin grafting, extra complications included (partial) necrosis of the graft (1–3.5%) and hair growth in the neovagina (1–6%). Peritoneal vaginoplasty yielded neovaginal granulation tissue (9%). Persistent discharge (3%) and vaginal prolapse (3%) were only apparent after bowel vaginoplasty. In general, reported complications rates were higher in studies where previous treatment (surgery or dilation) had failed, and even higher after surgery as a first-line treatment compared with after dilation for most main complications associated with the respective techniques.

**Functional success**

There is more variability regarding the definitions of functional success, although most seem to include the notion of ‘full genital performance during heterosexual intercourse as the essence of sexual functioning’
Figure 2  Literature review of the management of vaginal hypoplasia. *In some reviewed studies the outcomes of different treatment modalities were separately discussed and as such counted as separate studies. Note: See Supplementary data, Tables SI–SIII for numbered references.
<table>
<thead>
<tr>
<th></th>
<th>Traction vaginoplasty</th>
<th>Intestinal vaginoplasty</th>
<th>Peritoneal vaginoplasty</th>
<th>Vulvavaginoplasty</th>
<th>Skin flap vaginoplasty</th>
<th>Modified McIndoe procedures</th>
<th>McIndoe procedure</th>
<th>Vaginoplasty without grafts</th>
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<tbody>
<tr>
<td><strong>N patients</strong></td>
<td>837</td>
<td>912</td>
<td>393</td>
<td>286</td>
<td>171</td>
<td>154</td>
<td>1720</td>
<td>209</td>
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<tr>
<td><strong>Diagnosis</strong></td>
<td>98% MRKH</td>
<td>85% MRKH</td>
<td>98.5% MRKH</td>
<td>100% MRKH</td>
<td>83% MRKH</td>
<td>96% MRKH</td>
<td>92% MRKH</td>
<td>88% MRKH</td>
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<tr>
<td></td>
<td>2% CAIS</td>
<td>8% CAIS</td>
<td>1.5% MRKH or AIS</td>
<td></td>
<td>2% AIS</td>
<td>2.6% AIS</td>
<td>4.3% AIS</td>
<td>1.5% AIS</td>
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<td></td>
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<td></td>
<td>8% vaginal agenesis</td>
<td>1.4% cervicovaginal agenesis</td>
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<td>8% vaginal agenesis with</td>
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<td>and small uterus</td>
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<td></td>
<td>4.5% trauma (e.g.</td>
<td>0.9% uterovaginal atresia</td>
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<td>2.5% other (chromosomal</td>
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<td></td>
<td></td>
<td>oncological resection)</td>
<td>Note: Excluding (41; 46)</td>
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<td>anomalies, male</td>
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<td></td>
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<td>1% AIS</td>
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<td>pseudohermaphroditism)</td>
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<td></td>
<td></td>
<td></td>
<td>3.5% intersex (mixed</td>
<td>Note: Excluding (41; 97;</td>
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<td>'Normal' vaginal depth'</td>
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<td></td>
<td>GD or CAH)</td>
<td>46; 275; 11; 186; 151)</td>
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<td>(≥ 7 cm) (206; 314; 279;</td>
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<td>202; 111): 96% 'Good/adequate': 71.5% (11; 41)</td>
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<td><strong>Anatomical success (%)</strong></td>
<td>99</td>
<td>95</td>
<td>92</td>
<td>97</td>
<td>91</td>
<td>96</td>
<td>83</td>
<td>93</td>
</tr>
<tr>
<td><strong>Definition</strong></td>
<td>≥6 cm, except ≥10 cm in (112)</td>
<td>≥6 cm: 82% (114; 70; 129; 197; 107; 44)</td>
<td>≥8 cm: 100% (75; 294; 76; 200; 137)</td>
<td>Complete epithelization of the neovagina: 100% (23)</td>
<td>No shrinkage: 100% (336) (100%)</td>
<td>Not further specified: 97.5% (315; 289)</td>
<td>≥7 cm: 100% (22; 110; 295; 4; 304)</td>
<td>Sufficiently spacious: 70–95% (101; 158) Fine cosmetic result with normal angle: 100% (132; 256; 3) No scar and polyloid formation or contracture (308; 225; 254): 63–92% Normal epithelization of the vagina and ≥7 cm for amnion procedures: 97% ≥ 6 cm for interceed procedures: 94% ≥ 8 cm for buccal mucosa procedures: 100% ≥ 7 cm: 89% (211; 300; 72; 102; 171; 174; 12) ≥ 8 cm: 92% (151; 173; 204) ≥ 10 cm: 83% (186; 243; 7; 244) Max 25% contracture: 82% (35; 41; 97; 268; 11; 282) 'Normal' vagina: 33–100% (320; 164) 'Good' or 'adequate' result: 89% (108; 46; 38; 17; 29; 297) Successful take of the graft: 96% (61; 153; 282; 120) No contractures: 91% (319; 286; 51) Max 25% contracture of vaginal space': 50% (46) 'Normal' vaginal depth' (≥ 7 cm) (206; 314; 279; 202; 111): 96% 'Good/adequate': 71.5% (11; 41)</td>
</tr>
<tr>
<td><strong>Main intraoperative complications: proportion of patients</strong></td>
<td>Intraoperative Rectal or bladder injury: 1.8% Hemorrhage: &lt; 1%</td>
<td>Intraoperative Rectal, urethral or bowel injury: &lt; 1% Hemorrhage: 1%</td>
<td>Intraoperative Rectal, urethral or bladder injuries: 3.8% Hemorrhage: None</td>
<td>Intraoperative None</td>
<td>Intraoperative Hemorrhage: 1.3% Rectal or bladder injury: 1.9%</td>
<td>Intraoperative Hemorrhage: &lt; 1% Rectal perforation: &lt; 1%</td>
<td>Intraoperative Hemorrhage: 1.9% Bowel injury: &lt; 1%</td>
<td></td>
</tr>
</tbody>
</table>
Post-operative infections: 2.1%
Vaginal synechiae: 1.2%
Hematuria; Necrosis; Dehiscence; Fistulae; Stenosis: < 1%
Post-operative introital stenosis: 9.5%
Mucosal prolapse: 3.1%
Vaginal discharge: 2.9%
Post-operative neovaginal vault granulations: 8.7%
Strictures, stenosis or contracture: 5.1%
Rectovaginal or vesicovaginal fistulae: 1%
Postcoital bleeding: 1%
Urinary retention: 1%
Haematoma; Fever and abscess; Persistent discharge; Abdominal migration of mould: < 1%
Note: Most of these complications occurred in n = 5, in two older studies (35; 237). Intestinal obstruction only occurred in women who had had previous surgery. In studies in which women had previous surgery, higher stenosis and discharge complications (9 and 3%) were reported, compared with studies without previous surgery (4% and 1%). Prolapse complications were the same (3%).

Post-operative vaginal narrowing and scar formation: 5.8%
Hair growth: 5.8%
(Partial) necrosis of the graft: 3.5%
Fistulae: 2.3%
Infection: 2.3%
Note: No complications were reported in studies in which women had previous failed dilation therapy.

Post-operative urinary tract infections: 4.5%
Strictures: 3.9%
Only in amnion group: Rectal injury: 2%
Labial inflammation: 3%
Only in buccal mucosa group: Hemorrhage: 9.5%
Note: Urinary tract infections were higher in studies with previous treatment (after failed surgery 12.5%, after no previous treatment 3% and 3% after no previous treatment), but no differences were found regarding strictures (respectively, 6.3% and 5.4%, versus 6.6%).

Post-operative wound opening: 3%
Protruding hairs: 1%
Haematoma; Infection: 1%
Note: No complications were reported in studies in which women had failed surgery and vaginal infections (11 versus 3.6%) compared with studies in which women did not have surgery before. In studies with failed vaginal dilation before surgery, 3% of strictures were reported, and urinary tract infections and fistulae were present in respectively 2 and 3.5%

Proportion of patients with sexual activity 96%
Sexual activity 70%
88% 93%
Functional success 96%
90% 93% 95%

Functional success 96%
90% 93% 95%

Note: the majority (77%) already had previous surgery
<table>
<thead>
<tr>
<th>Definition</th>
<th>Traction vaginoplasty</th>
<th>Intestinal vaginoplasty</th>
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<th>Modified McIndoe procedures</th>
<th>McIndoe procedure</th>
<th>Vaginoplasty without grafts</th>
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<tr>
<td>Failure to dilate:</td>
<td>Satisfactory intercourse without dyspareunia: 96%</td>
<td>Satisfactory intercourse without difficulties: 90%, (41; 46; 318; 200; 148; 302; 274; 109; 188; 291; 134; 249; 53; 69; 159; 176; 245; 335; 170; 332; 49; 44; 333; 92)</td>
<td>Married sex life: 100% (207)</td>
<td>Satisfactory intercourse: 95% (108; 46; 239)</td>
<td>Satisfactory intercourse: 91% (22; 130; 304; 225; 3)</td>
<td>Pleasurable sexual intercourse, without dyspareunia and lubrications problems, and validated questionnaire scores comparable to controls (85; 114).</td>
<td>Satisfactory sexual intercourse</td>
<td>Satisfactory intercourse (no dyspareunia), without partner complaints (164; 173) or differences with a control group (259)</td>
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<td></td>
<td>Satisfaction with non-coital activities and pleasure: 100% (183; 34)</td>
<td>Only in two studies Satisfactory intercourse reported (110; 256), in which</td>
<td>Normal heterosexual relationships: 98% (75; 294)</td>
<td>Intercourse without dyspareunia or vaginal dryness: 94%</td>
<td>Functional success: 95% (225; 254)</td>
<td>‘Normal or successful sex life’: 100% (244; 153; 61; 275; 282)</td>
<td>‘Satisfaction with sexual function’: 67% - 100 (328; 17; 204)</td>
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<td>Satisfying marriage or ‘very good quality of sexual relations’ (311; 112): 55–100%</td>
<td>Only in one study results were 0% over the whole line (8)</td>
<td>Same FSFI scores as controls: 90% (70; 129; 197; 23).</td>
<td>Note: Only in one study results were 0% over the whole line (8)</td>
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<td>‘Normal or successful sex life’: 100% (244; 153; 61; 275; 282)</td>
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<td>Significant increase of penetration and satisfaction scores for both partners (94; 93): 100%</td>
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<td>‘Satisfaction with sexual function’: 67% - 100 (328; 17; 204)</td>
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<td>Post-operative dilation management</td>
<td>Advised post-operative dilation in (41; 81; 199; 44; 318; 53; 119; 39; 335; 322; 49; 333;238;23;170; 148; 84; 207):</td>
<td>Anatomical success: 97%</td>
<td>Sexual activity: 70%</td>
<td>Functional success: 93%</td>
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<td>A tendency of strictures could be overcome in patients who dilated (183; 125; 33; 104), but occasional problems with</td>
<td>Sexual activity: 70%</td>
<td>Functional success: 93%</td>
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<td>vaginal bleeding were reported (166)</td>
<td>Functional success: 93%</td>
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<td>Anatomical success: 97%</td>
<td>Sexual activity: 70%</td>
<td>Functional success: 93%</td>
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<td>Sexual activity: 82%</td>
<td>Functional success: 95%</td>
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<td>Functional success: 95%</td>
<td>Functional success: 90%</td>
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<td>Previous failed vaginal reconstruction</td>
<td>Surgery: 0.4% (312, 175)</td>
<td>Anatomical success: 100%</td>
<td>Anatomical success: 95%</td>
<td></td>
<td>Functional success: 100%</td>
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<tr>
<td></td>
<td>Anatomical success: 100%</td>
<td>Sexual activity: 83 – 100%</td>
<td>Sexual activity: 95%</td>
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<td>Functional success: 100%</td>
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<td></td>
<td>Functional success: 100%</td>
<td>Sexual activity: 75%</td>
<td>Sexual activity: 89%</td>
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<td>Functional success: 92%</td>
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<td>Dilatation: 0.1% (172)</td>
<td>The woman had neither sexual intercourse nor regular use of vaginal dilators as advised</td>
<td>Sexual activity: 0%</td>
<td>Functional success: 0%</td>
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<td>Dilation: 1.5% (8)</td>
<td>Anatomical success: NR</td>
<td>Sexual activity: 0%</td>
<td>Functional success: 0%</td>
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<td>Surgery: 2.8% (315; 289; 129; 70; 8)</td>
<td>Dilation: 5% (164)</td>
<td>Anatomical success: 100%</td>
<td>Sexual activity: 100%</td>
<td>Functional success: 86%</td>
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<td>Dilation: 5% (164)</td>
<td>Anatomical success: 100%</td>
<td>Sexual activity: 100%</td>
<td>Functional success: 86%</td>
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<td>Surgery: 2% (101; 110)</td>
<td>Anatomical success: 95%</td>
<td>Sexual activity: 95%</td>
<td>Functional success: 93%</td>
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<td>Surgery: 3% (10; 229; 163; 335)</td>
<td>Anatomical success: 100%</td>
<td>Sexual activity: 56%</td>
<td>Functional success: 93%</td>
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<td>Surgery: 3.4% (35; 216; 97; 98; 60; 327; 38; 11; 179)</td>
<td>Anatomical success: 76%</td>
<td>Sexual activity: 86%</td>
<td>Functional success: 88% Follow-up: 6.5 ± 8.5 years</td>
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<td>Surgery: 7.7% (11; 319; 206; 111)</td>
<td>Anatomical success: 85%</td>
<td>Sexual activity: 80%</td>
<td>Functional success: 71%</td>
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<td></td>
<td>Anatomical success: 52%</td>
<td>Sexual activity: 72%</td>
<td>Functional success: 100%</td>
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</tbody>
</table>
### Review of surgery and dilation for vaginal hypoplasia

#### Table VII: Overview of the studies with FSFI results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaginoplasty</th>
<th>Vaginal Dilation</th>
<th>Mean Total FSFI Score</th>
<th>Mean Follow-up (years)</th>
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</thead>
<tbody>
<tr>
<td>Bean et al., 2009</td>
<td>96</td>
<td>93</td>
<td>30.2</td>
<td>20.7</td>
</tr>
<tr>
<td>Communal et al., 2003</td>
<td>90</td>
<td>100</td>
<td>30.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Ismail-Pratt et al., 2009</td>
<td>93</td>
<td>96</td>
<td>30.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Minto et al., 2009</td>
<td>90</td>
<td>96</td>
<td>30.2</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Note: Vaginoplasty studies included both surgical and non-surgical options, even if satisfactory, did not have better indicators of sexual wellness or sexual function than those who were untreated, suggesting an important role of other factors than treatment affecting sexual wellbeing in these women. Studies investigating other quality-of-life parameters suggested that psychological variables, such as depression symptoms (Poland and Evans, 1985; Ismail-Pratt et al., 2007; Djordjevic et al., 2011), doubts about female identity (Freundt et al., 1993; Vates et al., 1999; Communal et al., 2003) and body image problems (Smith, 1983), are still prevalent after treatment and that neither surgical or non-surgical options, even if satisfactory, solve all problems (Carrard et al., 2012). It is interesting in this respect that women who had undergone treatment still perceive their vagina as abnormal (Minto et al., 2003). The repercussions of a negative genital image on sexual satisfaction have been shown in the general population (Berman et al., 2003). Stable relationships and a good communication between partners were further suggested to be crucial contributors to overall sexual satisfaction, independent of neovaginal length or treatment (Lappo¨hn, 1995; Liu et al., 2000). As such, the importance of vaginal depth for satisfactory outcomes and the general relationship between anatomical and functional success remains difficult to determine (Klingele et al., 2003; Borruto et al., 2007; Ismail-Pratt et al., 2007; Kapczuk and Friebe, 2012). With regard to the FSFI evidence, sexual problems were not more common in studies in which a mean vaginal length of <6.6 cm was reported. However, it is unclear from these studies if individual women with a smaller vaginal length were sexually active and had lower functional outcomes. Methodological problems have been noted with the FSFI when...*
women report not to be sexually active in the last 4 weeks preceding the survey (Meyer-Bahlburg and Dolezal, 2007). In addition, standard instruments, such as the FSFI, might not be well-tailored to assess the specific situation of women with vaginal hypoplasia, suggesting that an improved research methodology is needed to fully assess the impact of the involved conditions and its management on sexual experiences and wellbeing.

**Quest for the optimal vaginoplasty technique**

Based on the currently available evidence, it remains difficult to determine the superiority of one vaginoplasty technique over the other. This is due to problems including differences in technical terms used to describe surgical techniques and their modifications over the years making grouping of methods challenging, the heterogeneous group of patients, and the unavoidable reporting bias of surgeons towards the techniques they are mostly experienced in. Another problem relates to the lack of concordance in recording the long-term outcomes and complications of the different approaches. A follow-up of <1 year seemed to be associated with less sexual activity and functional success, but the effect on anatomical success is unclear. It is possible that the severity of dyspareunia or adequate lubrication are inversely proportional to the time since operation, resulting from the progressive epithelization of the neovagina, a process that is almost complete after 1 year. By further considering surgical complications as independent primary outcomes, it is perhaps possible to further elucidate which complications, mainly intraoperative (bowel and urinary tract injury, bleeding) or post-operative complications (e.g. infection, haematoma, necrosis, need for second surgery), are important for the technique’s safety and for functional success (e.g. vaginal dryness, vaginal discharge, granulation tissue; McQuillan and Grover, 2014). The major complication rates (i.e. death and venous thrombo-embolic events) have anecdotally decreased since laparotomy has been phased out or reserved for only very difficult procedures. Despite significant advances over the past decades in surgical techniques and improved knowledge of the anatomy and innervation of the female genitalia, there is, at present, no evidence that newer techniques improve long-term outcomes.

In addition, anatomical (based on vaginal length) and functional success (based on coital activity) were not significantly lower in studies in which previous surgery or dilation had failed, although there was a trend towards more complications in these studies. It could also be that patients in whom previous treatment had failed were those with more complex inherent anatomical features to begin with. As such, it remains unclear if previous attempts at vaginal reconstruction jeopardize surgical success.

Moreover, there is a lack of a standardized approach in reporting the results of post-operative dilation management. In those studies that mentioned a proper post-operative dilation regimen, anatomical success rates were in general higher, and contractures and strictures (between 5 and 7%) could be overcome, even in bowel vaginoplasty where post-surgical dilation is generally said not to be necessary. Therefore, maintenance dilation seems to have an additive value, either with regular dilation or coital activity. Nuancing the need for maintenance dilation, however, success rates are, in general, also high in studies without post-operative dilation.

Finally, from the available evidence, it remains unclear if age at surgery is related to the outcomes or if there exits an optimal time window for the most favourable anatomical outcomes. The majority of women felt, however, that the appropriate time to undergo surgery was in adolescence (Parsons et al., 2002), seeming to underline that interventions can only be undertaken when the patient is emotionally mature and ready to engage in sexual activity (Capraro and Gallego, 1976; Alessandrescu et al., 1996; Schatz et al., 2005; Brucker et al., 2008; Fotopoulou et al., 2010) or marriage in some cultures (Thompson et al., 1957; Sarwar et al., 2010). It has also been suggested that a vagina is not necessary for a young girl prior to sexual intercourse (Creighton, 2004) and that early psychological problems related to regular post-operative dilation can be minimized by delaying surgery (Filipas et al., 2000).

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### Table IV Other influencing factors on anatomical and functional success rates in vaginal surgery studies.

<table>
<thead>
<tr>
<th>Hymen</th>
<th>Psychological counselling</th>
<th>Timing of treatment</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No studies specifically reporting the relevance of hymen in outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence hymen in (44; 164; 172; 64; 34; 104; 311; 312); highly variable results:</td>
<td>In &gt;50% of studies: psychological interventions recommended, but no suggestions as to what type or when to deliver</td>
<td>Preperty versus puberty in same study (all bowel vaginoplasty):</td>
<td>46,XX MRKH versus 46,XY CAIS</td>
</tr>
<tr>
<td></td>
<td>Psychological counselling (support group or individual counselling) (239; 183; 166; 112; 287; 327; 328; 179; 249; 159; 168; 143; 54; 228) versus no psychological counselling:</td>
<td>Anatomical success: both 100% (149), NR in (260; 240)</td>
<td>Vaginal length before surgery: 1.4 ± 1.1 versus 3.3 ± 2.6 cm (P = 0.03)</td>
</tr>
<tr>
<td>Anatomical success: 81–100%</td>
<td>Anatomical success: both 1.1%</td>
<td>Complications: more common in puberty group (240; 260; 149)</td>
<td>Vaginal length after surgery: 9.0 ± 1.9 versus 8.3 ± 2.9 cm</td>
</tr>
<tr>
<td>Functional success: 55–100%</td>
<td>Functional success: 89 versus 82%</td>
<td>Functional success: unknown versus 0% (260) → 100% (240), NR in (149)</td>
<td>Anatomical success: NR in group (240; 260; 149) versus 92% versus 95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13–18 years versus &gt;19 years (7) (McIndoe procedure)</td>
<td>Sexual activity: 81 versus 73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anatomical success: 66.7 versus 86.5%</td>
<td>Functional success: 90 versus 85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complications (graft infections): 53 versus 15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional success: 60 (33 for 13–15 years, 85% for 16–18 years) versus 71%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Older patients (&gt;30 years): more disappointing, possibly because of an alteration of tissue elasticity (34) (Vecchietti procedure)</td>
<td></td>
</tr>
</tbody>
</table>

See Supplementary data, Tables SI–SIII for numbered references.
In sum, the quest for the optimal surgical method continues, as no technique is completely without failure risk, and some have (still) high complication rates. In general, however, traction vaginoplasty seems to have the highest anatomical (≥6 cm, 99%) and functional success rates (satisfactory coitus, 96%), followed by peritoneal vaginoplasty (92% anatomical success and 93% functional success), whereas both split-thickness and full-thickness skin graft procedures and intestinal procedures have the lowest outcomes (83–95% anatomical success and 90–93% functional success). Traction vaginoplasty also has the lowest complication rate, suggesting it to be an appropriate surgical technique either as first-line treatment or after failed vaginal dilation.

**Effectiveness of vaginal dilation as first-line technique: a time-honoured practice?**

Combining data from published non-surgical series allows some important insights into relevant factors that may impact on daily clinical vaginal dilation practices and on decision-making in individual cases.
Table VI  Influencing factors on anatomical and functional success rates in vaginal dilation studies.

<table>
<thead>
<tr>
<th>Total duration of dilation treatment</th>
<th>Frequency of dilation</th>
<th>Age at start treatment</th>
<th>Vaginal length at start treatment</th>
<th>Hymen</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.6 (± 4.8 months; range 2 days – 60 months)</td>
<td>Frequency of dilation periods, not the total amount of minutes dilating per day (e.g. one time for 30 min versus three times for 10 min) positively associated with anatomical success (R = 0.514, P &lt; 0.05)</td>
<td>Positive association with anatomical success (R = 0.6, P &lt; 0.05) &lt;18 years (268; 266; 164; 329; 122; 205) versus &gt;18 years (116; 313; 30; 202; 59; 23; 221; 161; 13; 91); versus 1x/d (203; 213; 327; 161; 185; 313); Anatomical success: 15 versus 77%;</td>
<td>Positive association between start vaginal length and end vaginal length (R = 0.69, P &lt; 0.05)</td>
<td>Absence (30); Sexual activity: NR</td>
</tr>
<tr>
<td>Dilation ≤6 m (233; 221; 161; 163; 215) versus &gt;6 m (268; 202; 265; 5; 122)</td>
<td>POSITIVE ASSOCIATION WITH</td>
<td></td>
<td></td>
<td>Functional activity: 92%</td>
</tr>
<tr>
<td>Anatomical success: 73 versus 63%</td>
<td>POSITIVE ASSOCIATION WITH</td>
<td></td>
<td></td>
<td>Hymen, hymenal remnants or pseudo-hymen in (116; 311; 313; 265; 164) versus studies in which parameter was unknown: Anatomical success: 68 versus 71%</td>
</tr>
<tr>
<td>Sexual activity: 86 versus 73%</td>
<td>POSITIVE ASSOCIATION WITH</td>
<td></td>
<td></td>
<td>Sexual activity: 89 versus 71%</td>
</tr>
<tr>
<td>Functional success: 70 versus 57%</td>
<td>POSITIVE ASSOCIATION WITH</td>
<td></td>
<td></td>
<td>Functional success: 92 versus 67%</td>
</tr>
<tr>
<td>Note: dilator treatment was stopped after maximum 6 months of compliance, irrespective of results, or because no further elongation of the vaginal length was observed in (215; 202; 164)</td>
<td>POSITIVE ASSOCIATION WITH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Psychological counselling**

In 63% of studies

**Definition:**

Emotional support from sensitive physician, not necessarily psychiatric care: (46)
Meeting with successfully treated former patient: (160; 325)

**Input from nurse specialist and/or psychologist:** (325; 5; 233; 221; 161; 122; 42; 91; 215)

**Psychodramatic therapy:** (59)
Support group meetings: (266)

Not further specified: (313; 265; 329; 13)

Psychological counselling versus no psychological counselling:
Minimal amount of months dilating: 3.8 ± 3.2 months versus 1.4 ± 0.4 months, P < 0.05
Anatomical success: 74 versus 63% P > 0.05
Functional success: 70 versus 77% P > 0.05
Successful completion of treatment not dependent on psychological counselling (13) and not different between inpatients or outpatients (13)
The quality-of-life was high in groups who attended counselling and those who did not (177); however, mental health was poor compared with physical health (194) and scores for sexual depression, sexual anxiety and fear of sexual relations remained high compared with groups of non-affected women (194)

**Diagnosis**

46,XX MRKH versus 46,XY CAIS

Start vaginal length: 3.1 ± 0.5 versus 4.5 ± 2.1 cm
End vaginal length: 6.8 ± 1.8 versus 8.2 ± 0.8 cm
Anatomical success: 70 versus 79%
Functional success: 73 versus 44%

**Maintenance dilation**

No studies compared women who did and did not maintain dilation when not being sexually active regarding functional or anatomical outcomes
Only in two studies (116; 161) women without coitus were still dilating at the time of follow-up: vaginal length: 6.5–8.5 cm
Possible, sexual activity further lengthens the vagina (194), and a combination of dilators and intercourse improves both anatomical and functional success rates (266; 185; 13)
Maintenance dilation recommended: 2–3 times/week when no regular coitus (313; 202; 268; 59; 265; 161; 122; 204)
Motive: to avoid shrinkage of vagina
No further dilation recommended (325; 91)
Motive: when embarking in a relationship after a substantial absence of dilators or intercourse, women very quickly regain their original length, eventually after dilating for a short time (91)

**Anatomical success:** NR

**Functional success:** only assessed in small subgroup of women, reported in (233), with sexual problems (difficulties with maintaining lubrication, pain during intercourse)

See Supplementary data, Tables SI–SII for numbered references.

NR, not reported.
### Table VII  FSFI values after alternative vaginoplasty techniques, vaginal dilation and no treatment in women with vaginal hypoplasia.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>(270)</th>
<th>(42)</th>
<th>(194)</th>
<th>(42)</th>
<th>(194)</th>
<th>(227)</th>
<th>(167)</th>
<th>(314)</th>
<th>(44)</th>
<th>(49)</th>
<th>(84)</th>
<th>(53)</th>
<th>(85)</th>
<th>(114)</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>131</td>
<td>9</td>
<td>10</td>
<td>15</td>
<td>7</td>
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<td>18</td>
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<td>35</td>
<td>45</td>
<td>8</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Control</td>
<td>MRKH</td>
<td>MRKH &amp; 46,XY DSD</td>
<td>MRKH</td>
<td>MRKH</td>
<td>MRKH</td>
<td>MRKH</td>
<td>MRKH</td>
<td>MRKH</td>
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<td>Bowel</td>
<td>Wharton</td>
<td>Wharton</td>
<td>Bowel</td>
<td>Bowel</td>
<td>Bowel</td>
<td>Bowel</td>
<td>Bowel</td>
<td>Oxidized cellulose</td>
<td>Amnion</td>
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<td>Ref.</td>
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<td>(8)</td>
<td>(202)</td>
<td>(129)</td>
<td>(23)</td>
<td>(66)</td>
<td>(104)</td>
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<td>(194)</td>
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<td>(84)</td>
<td>(53)</td>
<td>(85)</td>
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<td>5</td>
<td>56</td>
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<td>MRKH and CAIS</td>
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<tr>
<td>Desire</td>
<td>4.1 (1.1)</td>
<td>3.8 (0.6)</td>
<td>4.9 (1.0)</td>
<td>3.9 (1.2)</td>
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<td>NR</td>
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<td>4.9 (1.3)</td>
<td>3.5 (1.8)</td>
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<td>5.7 (1.2–6)</td>
<td>5.1 (1.5)</td>
<td>4.2 (0.1)</td>
<td>5.2 (0.9)</td>
<td>NR</td>
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<td>NR</td>
<td>4.0 (0.7)</td>
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<tr>
<td>Orgasm</td>
<td>5.0 (1.2)</td>
<td>4.9 (1.0)</td>
<td>5.1 (1.1)</td>
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<td>Pain</td>
<td>5.5 (1.0)</td>
<td>5.0 (0.7)</td>
<td>NR</td>
<td>4.1 (2.2)</td>
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<td>NR</td>
<td>4.8 (1.0)</td>
<td>NR</td>
<td>5.3 (1.8)</td>
</tr>
<tr>
<td>Total FSFI</td>
<td>30.2 (6.1)</td>
<td>27.6 (4.8)</td>
<td>NR</td>
<td>23.9 (5.7)</td>
<td>NR</td>
<td>25.3 (8.0)</td>
<td>28.2 (10.8–36)</td>
<td>29.9 (4.3)</td>
<td>24.8 (1.2)</td>
<td>28.0 (3.1)</td>
<td>28.9 (11.5 –35.7)</td>
<td>30.0 (3.0)</td>
<td>32.5 (1.1)</td>
<td>30.0 (6.9)</td>
</tr>
<tr>
<td>% Sexual distress</td>
<td>NR</td>
<td>55.6</td>
<td>NR</td>
<td>57.1</td>
<td>NR</td>
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<td>NR</td>
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<td>85</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
</tr>
<tr>
<td>% FSD</td>
<td>NR</td>
<td>50</td>
<td>NR</td>
<td>62.5</td>
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<td>30</td>
<td>14.8</td>
<td>12.5</td>
<td>NR</td>
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<tr>
<td>Vaginal length (cm)</td>
<td>9.6 (1.5)</td>
<td>8.9 (2.6)</td>
<td>4.8 (2.6)</td>
<td>9.1 (2.7)</td>
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<td>13</td>
<td>NR</td>
<td>9.6 (2.1)</td>
<td>9.8 (1.7)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean (SD). DSD, disorders of sex development; FSFI (range 0–36, domain scores 0–6: higher FSFI values denote better sexual functioning), FSD, female sexual dysfunction; NR, not reported; Ref, reference. Note: See Supplementary data, Tables SI–SIII for numbered references.
Anatomical success
Surprisingly, start vaginal length was not significantly associated with anatomical success. This refutes the claims that success can only be achieved in women with an existing vaginal dimple of 2–3 cm (Jasonni et al., 2007). For this reason, women with CAIs and androgen synthesis disorders, who generally have a larger starting vaginal length, do not seem to have an advantage over women with MRKH. Of note, women above 18 years of age at the start of treatment had significantly higher anatomical success rates, which is probably related to motivational reasons. Dilation has to be actively managed by the patient and a sustained effort is required, while progress is slow (Liao et al., 2006). Therefore, we suggest dilator treatment only in women in whom motivation is high, for example when being in a current relationship or wanting to engage in sexual activity, which has also been shown to be an important factor in post-operative dilation management. With regard to frequency and duration of dilation treatment, it becomes clear that the best anatomical results were obtained when the frequency of dilation periods was high, suggesting that regular stretching is more beneficial than the actual total time of stretching. Total duration of dilator treatment seems not to be related to anatomical success. Although some studies (Wabrek et al., 1971; Ingram, 1981), including our own research group (Callens et al., 2014), suggested that the highest gain in vaginal depth was reached within 4–6 weeks, and that the gain thereafter is minimal, it is unclear from the available data if there exists an optimal window for gaining length. Unfortunately, despite compliance, which can be increased with psychological support (Alderson and Glanville, 2004; Edmonds et al., 2012), conservative therapy can fail (Liao et al., 2011; Michala et al., 2012). No conclusions so far can be drawn on the presence or absence of the hymen relating to failure of treatment (Kimberley et al., 2012), nor whether perineal skin is different from the vagina in its elastic characteristics. However, failed dilation therapy does not preclude anatomical (nor functional) success if vaginoplasty afterwards is necessary. Overall, complication rates were significantly lower within the vaginal dilatation groups when compared with the different vaginoplasty techniques, being its major advantage, but should be followed-up in the long-term as well. Displacement of the bladder neck might occur during vaginal lengthening, which may affect bladder function and cause urinary symptoms (Michala et al., 2012). Also, the creation of a vagina in this fashion does not preclude vaginal disease, and cases of vaginal intra-epithelial neoplasia and vaginal carcinoma have been described (Hopkins, 1987). To date 15 (case) reports of vaginal prolapse have been reported (Williams, 1976; Vecchietti, 1979; Buss and Lee, 1989; Peters and Uhler, 1990; Schaffer et al., 2002; Muir and Walters, 2004; Calcagno et al., 2010; Christopoulos et al., 2011; Fedele et al., 2011; Burns et al., 2012), which is still considerably less frequent than reported prolapse after vaginoplasty (e.g. bowel vaginoplasty; 3%). Finally, although no randomized control data exist regarding maintenance dilation, the available evidence suggests that continued dilation is needed to maintain patency in periods of coital inactivity.

Functional success
From the available evidence, total duration of vaginal dilator treatment might have a detrimental effect on sexual activity levels and functional success rates, suggesting that dilation therapy should perhaps be stopped after 6 months of compliance; moreover, because anatomical success seems thereafter not affected. While the reasons for decreased functional success are not entirely clear, it is possible that the emotionally charged nature of the dilation process may make it difficult for women to keep separating the long-term medical dilation treatment from ‘real sex’—with a possible disgust or withdrawal from sexual activities. Especially, younger women (<18 years) might be more vulnerable to such difficulties, as motivational issues are already more prevalent in this age group. This does, however, question the possible impact of the recommended maintenance dilation on psychological grounds. Furthermore, as in surgical series, the importance of assessing functional success in the long-term is confirmed, as there seems to be a decrease with a longer follow-up period. Although some researchers have suggested that psychosexual functioning levels and coping abilities improve with time (Hecker and McGuire, 1977; Wu et al., 2009), others—including our research group—have indicated that women continued to feel far from normal in the areas of sexual potency and reproduction (i.e. perceived loss of social role as potential mother, loss of sense of equality with peers), contributing to high emotional distress, in different ways and at different times (Holt and Slade, 2003; Liao et al., 2011; Callens et al., 2014). Continued long-term follow-up acknowledges the importance of developmental–temporal factors to the distress.

Given the physical and psychological challenges then of this lifelong condition, it is unlikely that these women will achieve complete normal sexual function (Liao et al., 2011) —whatever enlargement technique is used. Interestingly, however, women simultaneously reported relatively high levels of sexual difficulties and sexual ‘satisfaction’. Problems related to the definition of ‘satisfaction’ with sex—for whom and with what (i.e. intercourse)—were already mentioned. In addition, women with MRKH or CAIs might have learnt to be ‘satisfied’ with barely satisfactory sexual experiences—that is, the women might have felt that sexual difficulties were to be expected and thus that they should not be dissatisfied (Minto et al., 2003). Although this raises concerns about the powerful influence of the current cultural context in which (sexual) difference is still taboo, it also questions how treatment success should be further approached (Liao, 2003). Moreover, as it was shown in therapeutic work that few women with vaginal hypoplasia allude to pleasure as a reason for wishing to engage in sex but rather reasons related to ‘feeling’ and ‘acting’ normal through intercourse (Liao, 2007), assuming intercourse will be a central therapeutic goal for these women is likely to give misleading impressions of what constitutes a successful treatment outcome (Roen and Pasterski, 2013). A key message here is that—where earlier approaches may have considered ‘normative’ functions of the genitalia and relative absence of patient complaints as indicators of good outcomes—future approaches need to reformulate outcome evaluation and specifically raise a wider range of psychosexually oriented questions (Liao, 2007; Roen and Pasterski, 2013). A simple questioning on sexual ‘satisfaction’ is not a useful measure in these diagnostic groups.

Pitfalls in treatment success
Psychological profile and the effect of counselling
In general, an inaccurate evaluation of the emotional status before any treatment is suggested to lead to a poor result (Capraro and Gallego, 1976; Strickland et al., 1993), as it was made clear that most women were struggling with body image (Smith, 1983; Carrard et al., 2012), or felt anxious, socially unattractive, depressed or lacked self-control (Kaplan, 1968; Bryan et al., 1949; Langer et al., 1990; Coney, 1992). Psychological interventions, such as cognitive-behavioural group
therapy, in these women have been shown to be effective in reducing anxiety and feelings of depression (Weijenborg and ter Kuile, 2000; Heller-Boersma et al., 2009a,b). However, despite the expectancy that the probability of further positive, functional or anatomical, outcomes are maximized with psychological counselling, this could not be confirmed with the current data. The self-esteem, knowledge or interpersonal skills built up in therapy or by peer support did not seem to be—both immediately and in the long-term—translated to satisfying sexual relationships (Liao et al., 2006; Heller-Boersma et al., 2009b).

Despite counselling, some women still felt depressed and extremely insecure relating to others (Kaplan, 1968; Hecker and McGuire, 1977), which is possibly also reflected in rather low sexual activity rates in any treatment paradigm (85%). Findings from our group even showed an unexpected increase in emotional difficulties after a standardized dilation programme with input from a clinical psychologist (Callens et al., 2014).

The majority of participants refused psychological counselling after a few sessions because contact with psychologists was said to engender powerful ambivalent emotions of abnormality as well as feelings of failure in not coping with the condition. Contact with peers was said to be motivating during treatment, but was further limited to discussion of subjects related to the shared condition (Alderson et al., 2004). While the move to including psychological input in clinical teams specializing in DSD is significant, it is still open to negotiation how the psychologist’s role in certain situations allows for a substantive and worthwhile contribution. It is of utmost importance to gain additional experience concerning the format of acceptable and efficient psychological care and how to integrate it in the regular medical follow-up (Liao, 2003).

**Diagnosis effects**

The present review further underlines the importance of detailed reporting on diagnosis, as there are differential outcomes for women with 46,XY and disorders of androgen action or synthesis (mainly CAIS), and 46,XX MRKH.

Although no differences in anatomical outcomes were found, women with an 46,XY karyotype have a significantly larger start vaginal depth compared with 46,XX women (e.g. Ismail-Pratt et al., 2007). The question arises as to whether this is the reason why the majority of women with CAIS do not opt for vaginal reconstruction interventions. The prevalence of vaginal hypoplasia within a CAIS population has not extensively been studied. Owing to the action of fetal testicular anti-Müllerian hormone on the developing Müllerian ducts, it is hypothesized that CAIS might be associated with 25–33% loss of vaginal length (Minto et al., 2003). In this study, however, despite a wide range, an average loss of 66% was shown in women with CAIS who had no treatment or sexual activity yet [3.8 ± 2.2 versus 9.6 ± 1.5 cm in non-affected women (Lloyd et al., 2005)], contradicting previous studies (Wisniewski et al., 2000; Minto et al., 2003; Purves et al., 2008; Wilson et al., 2011), and perhaps indicating that only those women with CAIS with the shortest start vaginal length and/or who have not been sexually active yet seek medical advice. After treatment, length of the neovagina is not necessarily proportional to satisfactory outcomes and this topic should deserve more detailed investigation.

In contrast, functional success rates, with all reconstruction techniques, were in general significantly lower in women with a 46,XY karyotype compared with women with 46,XX. A high rate of impairment of desire and arousal and dyspareunia in women with CAIS has been shown before (Kohler et al., 2012), which could be due to the complete lack of androgens affecting libido and orgasm (Wisniewski et al., 2000; Minto et al., 2003) and/or lack of androgen imprinting on the brain (Kohler et al., 2012). Also, gonadectomy and the subsequent estrogen substitution therapy is sometimes said to lead to insufficient vaginal lubrication (Michala et al., 2012). However, this information is not recorded in most studies and it is difficult to surmise how it might have impacted upon the results.

**Theory informing practice**

What emerges from this overview of selected publications is that evidence for both physical and psychosocial outcomes in women with vaginal hypoplasia remains incomplete and uncertain. Some fundamental questions about whether, for instance, treatment harms genital sensitivity or produces acceptable cosmetic results according to the affected women themselves are still disputed (Bronseleer and Callens, 2013). How these issues interplay in individual situations may perhaps never be resolved definitively because the answer will always depend on too many variables: the woman’s individual anatomy and physiology, the clinician’s skills and judgment, the quality of post-operative care, the psychosocial resources available and their perceived usefulness, relationships within the family and the deeply subjective nature of satisfaction with sexual sensation and function as well as cosmetic outcomes (Tamar-Mattis et al., 2013). Women must have access to this balanced information in order to fully weigh the potential risks and benefits of treatment. Furthermore, as the medical literature lacks high-quality comparative outcome studies, no evidence-based treatment guidelines can be provided. Despite these limitations, however, with the obtained information concerning the results of current techniques, we are in a position to advance thinking and practice in this field in various ways.

**Recommended treatment algorithm in women with vaginal hypoplasia**

Figure 3 summarizes the treatment decision tree in women with vaginal hypoplasia. Because of the physically low complication rate and an overall success chance of 75%, vaginal dilation treatment (either with or without intercourse) as a first-line choice seems to be justified if women had no prior treatment (i.e. reconstructive surgery). Dilator treatment has not only benefits (e.g. preservation of vaginal tissue), but also barriers, which should not be minimized (Liao et al., 2006). Vaginal dilation is time-consuming and some patients find it distressing. Overall, the laparoscopic Vecchietti procedure, becoming more and more available in specialized centres, is considered an appropriate surgical option for the creation of a neovagina in patients who are poorly compliant and failed dilation therapy, or for those who do not want to start with vaginal dilation therapy. In addition, laparoscopic assisted uterovestibular anastomosis through the Vecchietti technique is also possible in those women with cervicovaginal agenesis and a functional uterus (Fedele et al., 2008a). It is difficult to justify proceeding directly to some of the more complex techniques, such as intestinal vaginoplasty, with its associated high morbidity and long-term side effects. These techniques can have a role in complex patients with previous extensive abdominally surgery, particularly those cases with significant scarring from previous surgery. Choosing the right operation in patients who require surgical reconstruction is integral to success. Moreover, it should be noted that the first attempt at any neovaginal reconstruction has the best chance for success and every failed
attempt leaves its traces and should be avoided. Therefore, it is crucial to resolve whether the patient has the mental resources, including perhaps certain personality traits, necessary to cope with the management of her condition in an effort to optimize therapeutic success (Coney, 1992). Regardless of the vaginal reconstruction technique used, patients should be managed in specialized centres by a multidisciplinary team, which can provide adequate emotional and psychological support. Specialist units should be able to offer all treatment options and also have a duty to provide detailed long-term outcome data (Michalaet al., 2007; Deanset al., 2010).

New ideas from old concepts: vaginal dilation treatment in clinical practice

A practical protocol, informed by the literature and our own experience, for the management of women with vaginal hypoplasia is provided in Fig. 4. A further individual-based approach with skilful evaluation and negotiation with the patient can help to prevent vaginal dilation treatment failure and limited compliance. Figure 5 illustrates how a vaginal dilation user model—based on a health belief model of behaviour change (Bonner et al., 2012), and on therapeutic interventions within a framework of cognitive-behavioural psychology and motivational interviewing (Miller and Rollnick, 1991; Liao et al., 2006; Ismail-Pratt et al., 2007)—would incorporate the influencing factors identified in this review. It provides useful pointers for understanding compliance difficulties with vaginal dilation and suggests that vaginal dilator use can be increased by

(i) Accounting for modifying factors before and during the course of treatment, such as diagnosis adjustment. Women may experience a range of symptoms consistent with posttraumatic stress disorder.

Psychological difficulties may act as a barrier to dilator treatment, or conversely, the dilator treatment may exacerbate pre-existing psychological symptoms (Edmonds et al., 2012) and must be delayed in the presence of psychological disorders (e.g. depression) (Alderson and Glanville, 2004). The further timing of treatment should be planned on an individual basis as there is considerable variation in psychosocial development and maturity. High motivation to start with sexual activity or a current relationship will benefit dilator use. It is suggested not to start dilator treatment before the age of 16 years, due to motivational issues, which are more prone in adolescence (Alderson and Glanville, 2004). Also, younger women may be less familiar with their genitalia or might have anxious reactions toward the idea of inserting an instrument in the vulvar region (Alderson and Glanville, 2004), the more so when dilators are perceived as highly sexualized objects (Cullen et al., 2012). For some women, negative genital perceptions may also be exaggerated by an idealization of ‘normal’, and negative social comparisons may raise the anxiety further (Liao, 2006a, b). Ideally, where appropriate, patients should be encouraged to access support from their personal contexts, as it enhances self-management in many chronic diseases (DiMatteo, 2004). However, because of the intimate nature of the syndromes, many women feel they cannot talk about it with family or friends and wish to hear about other patients’ experiences. Support groups can provide a useful resource for sharing concerns or motivation during treatment. Regular appointments with a clinical psychologist, nurse specialist and/or physiotherapist can provide opportunities for addressing other implications of the diagnosis, such as its effect on fertility or body/genital image and for problem-solving practical difficulties.

Figure 3 Decision tree for treatment options in vaginal hypoplasia.
(ii) Providing stronger cues to action, such as additional information (e.g., websites, easy-to-follow instructions boosting patient’s confidence to correctly use the dilators), and easy dilator provision (e.g., through the hospital pharmacy). Also, regular vaginal examinations by clinicians and personal experience of anatomical and functional success can act as confirmation of the efficacy of dilators. However, as vaginal size in non-sexual situations can be a poor predictor of pleasurable intercourse upon sexual arousal, clinicians should reduce the level of preoccupation with vaginal size solely and also emphasize sexual enjoyment.

(iii) Emphasizing the benefits (e.g., sexual function is possible by achieving greater vaginal length) and overcoming the barriers (e.g., having a sense that it is not right or natural to touch genitals or treatment triggers flashbacks to previous traumatic experiences such as unsuccessful attempts at intercourse) (Liao et al., 2006). The extent of a positive attitude towards treatment (i.e., benefits outweighing the barriers) and the perceived efficacy (i.e., personal beliefs of how likely it is that dilation will work) will be central to a woman’s motivation to repeat the exercises regularly (Alderson and Glanville, 2004).
Minimizing the perceived threat, such as pain during intercourse. Anxiety can lead to a higher anticipation of pain, thereby exacerbating pain by intensifying muscular spasms. Relaxation training and psychological pain management techniques in the treatment of dyspareunia associated with gynaecological conditions, such as vulvar vestibulitis, might be useful (Bergeron et al., 2001).

Remaining questions and future perspectives

The current review has highlighted the need for further investigations in a number of areas. First, a fuller awareness of a need to assess treatment outcomes (i) at various developmental timepoints, (ii) both qualitatively and quantitatively and (iii) with an improved research methodology including a wider range of psychosexual matters, such as the quality of intimate relationships, and partner-independent sexual activities. While it is of relevance in these groups of women to defocus on penile–vaginal intercourse and to discuss sexual intimacy in broader terms, the significance of coital activity is, however, still culturally reinforced and will therefore remain an important aspect of the clinical management and evaluation of women with vaginal agenesis for some time. Longitudinal studies, incorporating a head-to-head prospective evaluation of interventions, should be undertaken. The majority of studies evaluated had a retrospective design, and pretreatment measures were available for comparison only in a handful of studies (El Saman et al., 2007, 2011; Ismail-Pratt et al., 2007; Walch et al., 2011; Cao et al., 2012; Michala et al., 2012). Comparing pre- and post-treatment results, specifically in the long-term, would provide a more precise indication of the effect of any treatment.

Secondly, reports on the associated anomalies have not been the major focus of recent papers on vaginal agenesis. No firm conclusions can be drawn about certain anatomical prerequisites for treatment success (e.g. presence of hymen), and further comparative studies between 46,XX women and 46,XY women with vaginal hypoplasia in different areas are highly valued. For instance, the relative contribution of hormonal factors in sexual dysfunction, in CAIS versus MRKH, has to be further elucidated. In addition, fertility considerations remain a challenging aspect. To date, it is difficult to reach any conclusion about the potential clinical pregnancy rate in women with MRKH, after ART and gestational carriers, as national or international databases recording this type of information are non-existent and numbers in the published series are relatively small. Successful reports on uterine transplants open up the future possibility of this form of treatment, but also raise ethical issues. Given the considerable variability in Müllerian structures in patients with 46,XX MRKH, it is clear that all aspects of treatment require a tailored approach. In parallel, in women with a 46,XY karyotype individualized gonadal management is necessary.

Thirdly, the possibility of coital dilation should be further taken into consideration and explained to the patients as one of the available therapeutic procedures. The impact of further sexual activity post-treatment on anatomical outcomes needs further investigation, as this could not be confirmed in all studies.

Fourthly, additional experience has to be gained on how psychological input may impact on the processes of diagnosis and treatment. Psychotherapy might provide an exploration of alternatives to penetrative...
intercourse. Of note, the standard sex therapy for couples who experience difficulties with intercourse is to first of all abstain from it. Masters and Johnson (1970) advised couples to ‘sensate focus’ or (re)-discover a range of pleasurable activities together. However, the typical advice for a woman who has undergone vaginal reconstruction is that she must engage in regular intercourse or dilate indefinitely. This advice may be counterproductive for the woman and her partner (Liao, 2006a, b).

Finally, the rarity and (vaginal depth) variability in patients with vaginal hypoplasia precludes the establishment of strict guidelines regarding both non-surgical and surgical management. To our knowledge, this was the first review in which the outcomes of more than 30 vaginal dilatation treatment studies were under scrutiny, compared with outcomes of both non-surgical and surgical management. To our knowledge, this was the first review in which the outcomes of more than 30 vaginal dilatation treatment studies were under scrutiny, compared with outcomes of more than 190 surgical studies. The low rate of physical complications associated with dilator treatment should not lull us into prescribing a treatment that may not be effective and dilatation treatment should be further subjected to the same scrutiny as any other intervention (Liao et al., 2006). Routine data collection, driven by patients’ lived experiences, is the key marker of care quality and should inform improvement strategies. Meanwhile, with proper care, might we begin to think of the vagina as Oliver Wendell Holmes once viewed the mind: Man’s mind, once stretched by a new idea, never returns to its original dimensions (Frank, 2001, p. 508).

**Supplementary data**

Supplementary data are available at http://humupd.oxfordjournals.org/.

**Authors’ roles**

N.C. and M.C. conceived the study, and participated in study design, collection and analysis of data, and drafting and revising of the manuscript and critical discussion. G.D.C, S.W., S.M. and P.H. participated in revising of the manuscript and critical discussion. All authors gave final approval of the manuscript to be published.

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**References**


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**References**


