

## Diagnostic tools for female urethral diverticulum: Current perspectives

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### Abstract

Although once considered quite a rare condition in the past, female urethral diverticulum (UD) would now appear to have a higher frequency, perhaps due to greater attention from physicians. To date, there is no agreement on which is the best method for diagnosis of female UD. Traditionally, the approach was based on quite invasive techniques, such as voiding cystourethrography, and double-balloon urethrography, with satisfactory results but relevant limitations. More recent high-resolution imaging techniques, such as 2D-3D ultrasonography (US) and magnetic resonance imaging (MRI) have also been applied in the study of the abnormalities of the female urethra. US had the advantage of the outpatient setting, non-invasiveness and absence of contrast medium use; MRI, is characterized by high sensitivity thanks to multiplanar capability, with an optimal characterization of periurethral diseases or its abnormalities, and lack of ionizing radiation. A real innovation is represented by computer tomography-voiding cystourethrography, a rapid technique that allows for high quality simultaneous 2D and 3D images of the urethra, well correlated to MRI and consequently with surgical results. Here, we report and comment the available tools in the diagnosis of female UD, focusing particularly on pros and contra of different methods.

### Introduction

Female urethral diverticulum (UD) was first described in medical literature in 1805 by William Hay.<sup>1</sup> It is defined as a localized sac-like herniation, continuous with the ure-

thral lumen, between the periurethral fibromuscular fascia and anterior vaginal wall.<sup>2</sup> A population-based analysis in Olmsted County (USA) reported a low incidence affecting fewer than 20 women out of 1,000,000, with an incidence of 0.02% per year.<sup>3</sup> Although considered quite a rare condition in the past, female UD seems to have much more frequent occurrence today, perhaps due to greater attention from physicians, with a current prevalence estimated between 0.6 and 6.0%.<sup>4-6</sup>

The etiology of acquired UD is still to define. In most cases, a congenital origin is attributed and major incidence is in the third to fifth decade.<sup>6,7</sup> The majority of UD are located in the middle third of the urethra and involve the postero-lateral wall, resulting from enlargement of obstructed periurethral glands.<sup>8,9</sup> Periurethral glands are located in the distal two-thirds of the female urethra terminating in the paraurethral glands of Skene (variable in number from 6 to 30): all paraurethral ducts empty secretions into the urethral lumen. Possible causal factors of UD formation include urethral injury during childbirth, previous surgery and repetitive trauma.<sup>10</sup>

Approximately 20% of patients with UD are asymptomatic and the symptoms, when present, do not seem to be related to the size or number of diverticula.<sup>11</sup> UD may be small (4-5 mm) or large (until 3 cm or more), single or multiple, round shaped or circumferentially or horseshoe shaped. Dysuria, post-void dribbling, dyspareunia, recurrent urinary tract infections, periurethral mass on physical examination are the most common symptoms and findings of UD.

Complications of UD can occur, including abscess, intra-diverticular calculus and, less commonly, neoplasm.<sup>7</sup>

For these reasons, UD diagnosis is often not easy, and it is estimated that the mean time from onset of symptoms and UD diagnosis is about 24 months.<sup>12</sup> Thus, the most important factor for UD diagnosis is to actually think of it and, consequently, look for it. While clinical history and physical examination are the first diagnostic steps, imaging is at the same time important to confirm the findings of clinical evaluation or to find UD without clinical evidence.<sup>13</sup>

To date, there is no agreement on which the best diagnostic method is for female UD. The older, traditional and more invasive techniques used are voiding cystourethrography (VCUG), double-balloon urethrography (DBU) and urethro-cystoscopy (UC).<sup>14-16</sup> Recently, the high-resolution imaging techniques, such as 2D-3D ultrasonography and magnetic resonance imaging (MRI), have also been applied in

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the study of the abnormalities of the female urethra, with high sensitivity and less invasiveness. Here, we report and comment the available tools in the diagnosis of UD, focusing particularly on the current role of VCUG.

### Voiding cystourethrography

VCUG is the oldest and most traditional instrument to diagnose female UD, considered as the imaging modality of choice providing data regarding the number, location, and size of the UD as well as communication with the urethra.<sup>17</sup> In the past, many authors supported the efficiency of this approach: Ganabathi *et al.* in 1994 demonstrated the presence of UD in 95.2% of a large series of 63 women using VCUG.<sup>18</sup>

The VCUG procedure is technically easy and simple.<sup>19</sup> With the patient in the standing position and using a 14-F Foley catheter, the operator fills the bladder with contrast agent. Although 15% dilution of

ionic contrast medium diatrizoate meglumine produces good images, a non-ionic contrast medium (*Omnipaque*<sup>TM</sup> or *Ultravist*) is generally preferred.

Technically, it is important to achieve the anteroposterior and oblique images of bladder and urethra during filling as well as during voiding and after voiding: when UD is present, the images obtained during (Figure 1) or after voiding (Figure 2) can generally demonstrate total or partial filling of the diverticular sac. Moreover, filling defects within diverticula may suggest the possibility of urethral calculi or tumors.<sup>7</sup> The voiding phase of intravenous urography, although useful for the diagnosis of duplex system with ectopic ureterocele, is nowadays performed with ultrasound, CT and MRI studies. However, VCUG has some known limits: the procedure is invasive, and time consuming, the patient is exposed to ionizing radiations and requires catheterization.<sup>19</sup> Furthermore, successive and more recent experiences reported far less favorable UD detection rates, questioning the VCUG role as principal diagnostic tool.<sup>20,21</sup> In particular, low accuracy in the definition of the precise localization of the diverticular orifice was highlighted, as well as in the correct identification of number and size of UD, mainly when the UD is only partially opacified.<sup>22</sup> In 2003, Golomb *et al.* published the results of a comparison between the information obtained by VCUG and positive-pressure DBU on 12 women with a presumptive clinical diagnosis of UD, in order to verify which imaging modality can better delineate the features of the diverticula.<sup>19</sup> In 4 out of 12 patients (33.3%), VCUG completely failed in showing the diverticulum, whereas DBU showed a large complex diverticulum in 2 patients and a distinct mid-urethral diverticulum in 2 patients; in the remaining 8 women (66.7%), VCUG delineated only the lower part of the diverticulum, whereas DBU depicted a large diverticulum extending beneath the bladder neck in 3 patients and multiple diverticula in 5 patients. The sensitivity of DBU and VCUG, was defined therefore at 100 and 66.7%, respectively.<sup>19</sup>

Based on the evidence of these recent comparative reports, VCUG results have been equivocal or non-confirmatory, and often needed additional imaging studies; in this sense, and considering the availability of other effective diagnostic options, the VCUG could be used mainly as a screening test, and if it fails to provide adequate characterization of the UD, one of the other imaging modalities could be applied.<sup>17</sup> Finally, VCUG may be a useful tool for the contemporary diagnosis of an eventual vesical-urethral reflux – a possible cause of per-

sistent urinary infection like UD – and, when it is performed during a video-urodynamic investigation, in order to evaluate bladder dysfunction such as incontinence, hyperactivity and obstruction, which are often the cause of symptoms, and the underlying mechanism of UD genesis.

### Double-balloon urethrography

The first DBU was performed and reported in 1959.<sup>23</sup> DBU is a positive pressure retrograde urethrography and to perform this procedure, it is necessary to use a specialized 14-F Foley catheter with a second balloon or a retention plug proximal to the balloon at the catheter tip: the passive bladder filling with contrast agent is obtained at a higher pressure.

In particular, the bladder balloon is filled to 20 ml to close the bladder neck; the second balloon, running to the catheter, is placed close to the external urethral meatus; the catheter between the balloons is open and, in this way, the contrast medium can be injected into a closed camera, realizing a positive pressure urethrography. It is important that the operator ties the balloons in the right position during the examination.<sup>19</sup>

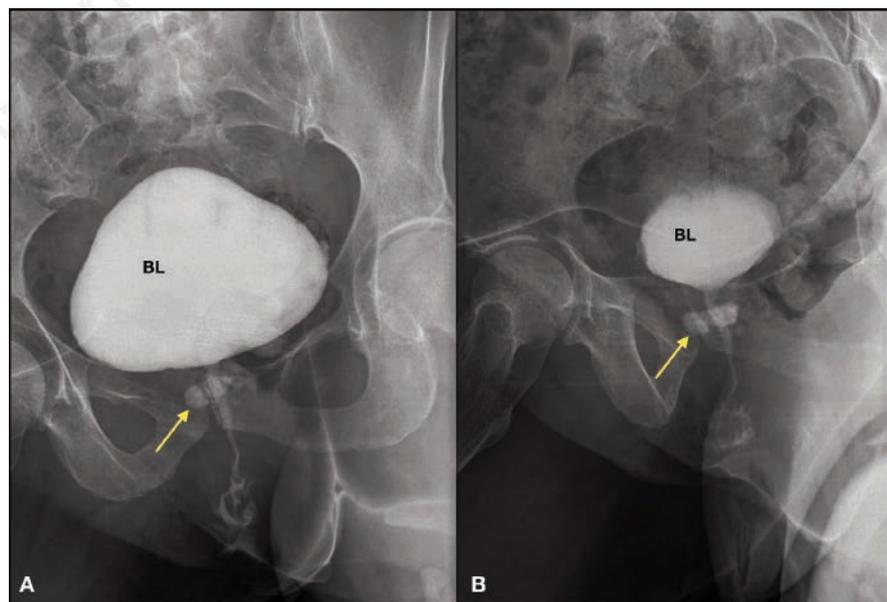
In comparison with VCUG, the DBU technique has an *extra weapon* as it works under positive pressure. The positive pressure, in fact, allows to force contrast agent into a diverticular orifice during the injec-

tion and can be identified at early phase of filling of the UD.<sup>24</sup> In this sense, the reason why VCUG fails in some patients while DBU is successful may be due to a narrow communication of the diverticulum to the urethra, which, during normal voiding, blocks the viscous contrast medium from entering the diverticulum, whereas the positive-pressure created during DBU overcomes the resistance and enables proper visualization of the diverticulum.<sup>19</sup>

Although DBU has proved to be more sensitive than traditional VCUG as a diagnostic test for female UD,<sup>19,24</sup> it has several limitations.<sup>24,25</sup> It is technically more challenging to perform than VCUG, with the technical difficulty of creating an ideal *closed urethral system* by the catheter; the procedure may be painful for the patient and exposes the patient and operator to ionizing radiation.<sup>26,27</sup> Moreover, increased risk of urinary tract infection and/or urethral injury have led to a drop in the usage of this procedure.<sup>27</sup>

### Ultrasonography

Transabdominal, transrectal and transperineal techniques have been described in the last few years for the assessment of UD, but despite their non-invasiveness, these approaches are not widely diffused in routine practice, mainly because of the insensitivity for detecting



**Figure 1.** A 52-year-old woman with recurrent urinary tract infections. On physical examination a periurethral mass was present with expression of pus from the urethra. (A) VCUG showed a diverticulum in the middle urethra; (B) the bladder is almost completely voided and the diverticulum is seen surrounding the urethra in a horseshoe shape (BL: bladder; yellow arrow: urethral diverticulum).

small diverticula (<2 cm).<sup>10,28</sup>

Transvaginal US (TV-US) (7–10 MHz) has also been tried for the study of urethra and abnormalities, with better results, being able to detect UD that do not fill with contrast agent. With this approach, the urethra is fully visible from the meatus to the bladder neck in different planes, and additional information on UD characteristics (size, number, site, content) may be achieved.<sup>29</sup> The advantages of US include absence of ionizing radiation, wide availability, ability to differentiate the type of mass (solid vs cystic) and the precise relationship of the diverticulum to the urethra; finally, it is the imaging method of choice for pregnant patients with suspicion of urethral pathology. However, TV-US has the relevant disadvantage of involving direct urethral compression as well as poor resolution for deep soft tissue, inter-operator variability, and differentiating UD from other peri-urethral cystic diseases.<sup>5,10</sup>

Referring to US techniques applied to urogynecology, a *new entry* is the translabial ultrasound (TL-US) approach, which has proved to be a valid option in the study of disorders of the lower urogenital tract.<sup>30</sup> To perform a correct TL-US evaluation, the principal procedural phases are the following: i) probe placement on the anterior vulvar commissure (directed to the anterior vaginal wall), firstly on the median sagittal plane under the pubis; ii) initial image acquisition (sagittal plane), showing the arcuate ligament of the pubis, the bladder with bladder neck and the longitudinal section of the urethra; the arcuate ligament of the pubis appears as a hyperechoic image and is a crucial landmark; the urethral lumen appears as a transonic channel bounded by hypoechoic outline; iii) image acquisition on the coronal plane (rotating the probe 90° anti-clockwise), focusing on the urethral lumen and any eventual abnormalities<sup>5</sup> (Figure 3).

The periurethral mass may be easily detected and its echogenicity evaluated: a neoformation is defined as UD only if a communication channel to the urethral lumen is identifiable. In 2009, El-Zein *et al.* reported their experience in locating the UD neck intra-operatively, in patients in which cystoscopy had failed: they showed the relevant role of TL-US as a diagnostic tool and as surgical guidance, identifying 95% of the UD without the help of level II diagnostic methods.<sup>31</sup> Then, Gugliotta *et al.*, in 2015, suggested the use of TL-US as a first-line method for the evaluation of urethral masses in an outpatient setting, especially when UD is clinically suspected, also focusing on the sonographic characteristics in differential diagnosis with the para-urethral and

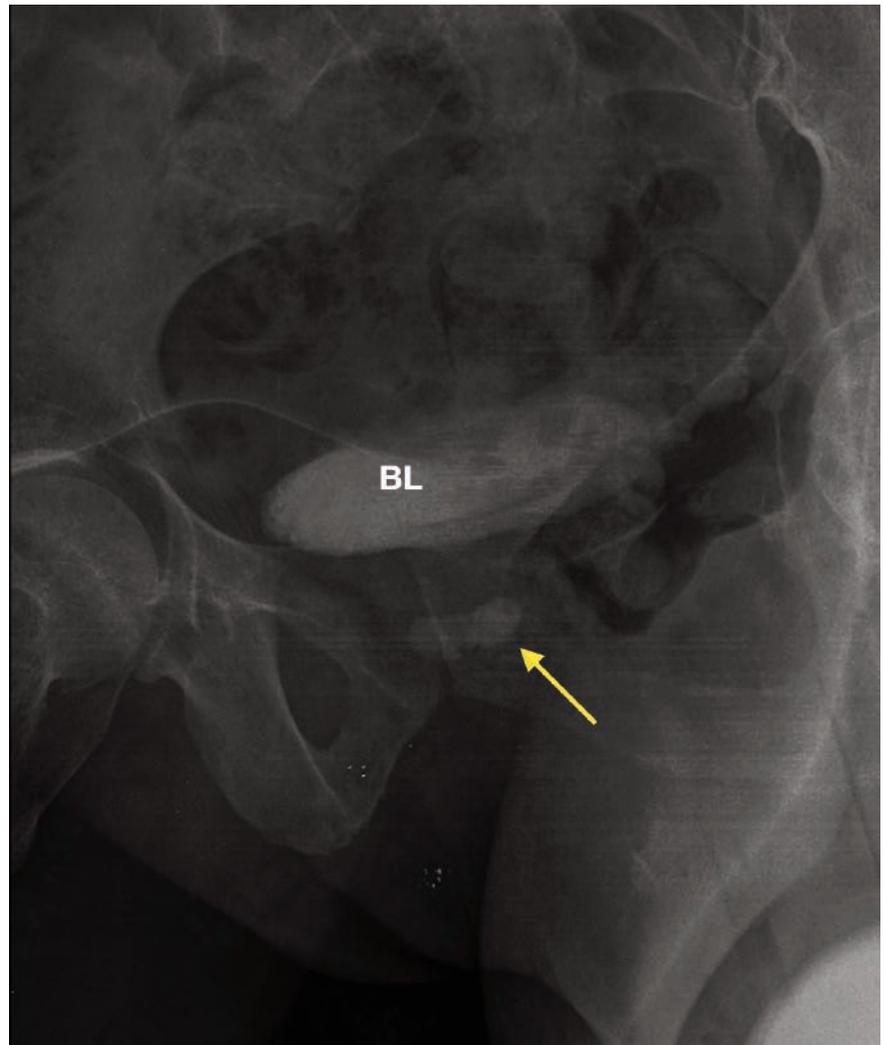


Figure 2. The diverticulum is clearly seen in after voiding film (BL: bladder; yellow arrow: urethral diverticulum).

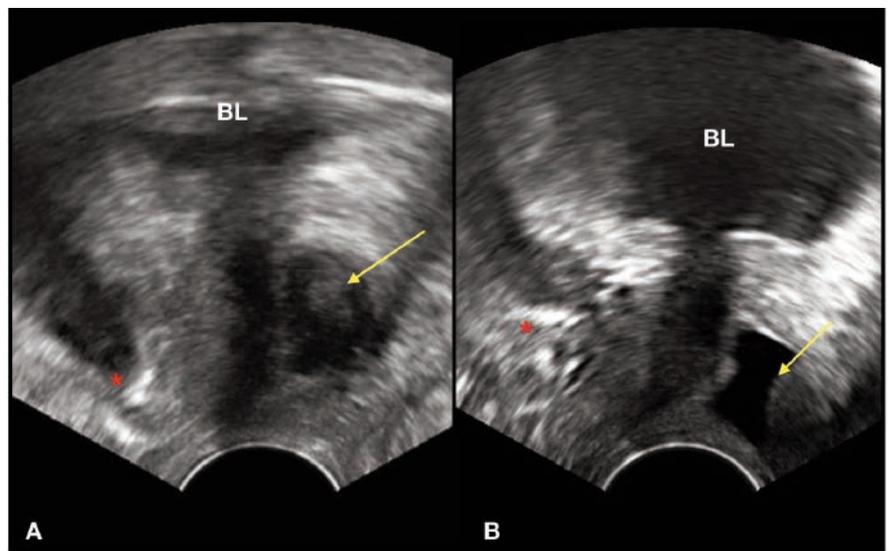


Figure 3. Trans-labial ultrasound of a simple (A) and complex (B) urethral diverticulum in longitudinal section (BL: bladder; yellow arrow: urethral diverticulum; red star: pubis)

vaginal cyst.<sup>5</sup> In addition to minimal invasiveness, TL-US allows to achieve the images from various angles of view, evaluating the spatial relationship of the UD to the urethra. Certainly, a skilled operator is necessary.

## Magnetic Resonance Imaging

MRI plays an important role in the evaluation of the urogenital tract and, in particular, urethral diseases in women. Literature is not extensive but other groups have reported almost 100% MRI sensitivity to diagnose UD.<sup>32-34</sup>

It may be performed with a torso phased-array coil or an endoluminal (endorectal, endovaginal, or endourethral) coil, thereby allowing improved signal-to-noise ratio and high-resolution imaging.<sup>35,36</sup> Female urethral examinations are performed on a 1.5-T MR imager with a pelvic phased-array coil. The suggested MRI protocol consists of axial, coronal, and sagittal fat-saturated fast spin echo T2-weighted sequences (repetition time msec/echo time msec = 4,000–5,500/80–120, three signals acquired, echo train length of 12, 18–24-cm field of view, 3–5-mm section thickness, no intersection gap, 512 × 512 matrix).<sup>7</sup>

The intravenous administration of contrast medium can be helpful in differentiating a condition of inflammation from malignancy in the context of a UD; possible malignancy arising from a diverticulum can be visualized as enhancing soft tissue within the diverticulum. On the other hand, endoluminal MRI is excellent for defining the characteristics of a lesion that involve the urethra: it has been able to confirm the presence of the orifice of the UD or assess the non-communication of the urethral mass.<sup>37</sup> This approach allows good recognition of the urethral diverticular cavity: single or multiple, unilocular or multilocular, internal acute inflammation or neoplasm (mainly after the administration of contrast agent); moreover, considering the soft-tissue contrast capacity, MRI adequately differentiates a solid mass from a complex diverticulum with septa (Figure 4).

The advantages of MRI include multiplanar capability, with an optimal characterization of female urethral and periurethral diseases or its abnormalities,<sup>38</sup> and lack of ionizing radiation. However, the main disadvantages include high cost and longer examination time.<sup>13</sup> It is worth noting that more recent experiences on the topic with the addition of surgical data seem to limit the paradigm that MRI is the gold standard to diagnose UD. Kim *et al.* evaluated the role of MRI in the diagnosis of UD in 20

patients showing sensitivity limited to 70% but with higher accuracy than VCUg and UC: 14 vs 11 out of 20 diverticula, respectively identified with MRI and VCUg/UC. Authors, however, highlighted that the use of MRI contrast medium is able to enhance the characteristics of the content of the UD, such as in showing granulation tissue or carcinoma.<sup>39</sup> Chung *et al.*, in 2010, reported a discrepancy between MRI and surgical findings in a sample of 76 patients who underwent diverticulectomy: in 41 patients who had previously undergone MRI, 10 (24.4%) were diagnostic errors (diverticula were not seen on MRI in 3 cases).<sup>32</sup> To explain these diagnostic errors, authors proposed different hypotheses; UD did not appear fluid filled on T2-weighted imaging and it is dynamic by nature with constant fluctuation in size. In this sense, a limitation of MRI is that it captures images at a single point in time, in contrast to more dynamic tests that capture real-time images, such as VCUg.<sup>32</sup> Some recent studies also show that MRI does not have excellent sensitivity in detecting ostia.<sup>32,33,40</sup> However, MRI is certainly a relevant tool to evaluate UD, especially in the pre-operative phase, but physicians should be aware of its limitations.

## New tools: computer tomography-voiding cystourethrography

Recent evolutions in multidetector CT have made 2D and 3D reformatted CT images available for several diagnostic fields.<sup>7</sup> The new-generation CT scanners (with faster scanning speeds) allowed urethral evaluation with new techniques as CT voiding cystourethrography (CT-VCUG) and virtual urethroscopy. In this field, the use of a 16-MDCT scanner is innovative, with a detector configuration of 0.75 mm~16 and a pitch of 1.25. The gantry is firstly positioned at the level from which the scanning starts (the top of the bladder) and then the patient is asked to void. When this signal is noticed, an unenhanced scan down to the inferior margin of symphysis pubis is achieved.<sup>21</sup> The scanning time is very fast (about 7 seconds). Axial images are reconstructed with a 1-mm thickness and interval; thin-slab (2-mm) coronal and sagittal images and 3D CT urethrographic images, as well as CT virtual urethroscopic images, are reformatted.<sup>21</sup>

The multidetector CT has several advantages in comparison with standard techniques: rapid scanning, thin collima-



**Figure 4. Magnetic resonance imaging (with contrast medium) of female urethral diverticulum (BL: bladder; yellow arrow: urethral diverticulum; red circle: pubis). Reproduced with permission from: Gugliotta G, Calagna G, Adile G, et al. Use of trans-labial ultrasound in the diagnosis of female urethral diverticula: A diagnostic option to be strongly considered. The Journal of Obstetrics and Gynaecology Research 2015;41:1108-14. doi:10.1111/jog.12676**

tion, and highly improved resolution of the z-axis; these technical characteristics allow the multiplanar and 3D reformatted images of high quality, comparable to those of conventional VCUG.<sup>7</sup>

This approach can show the accurate measurement of diverticulum size, the simultaneous viewing of 2D and 3D images of the urethra (without magnification or distortion) and the presence and exact location of the opening of the UD in the urethral lumen, and clearly visualize the neck; this last capacity makes the multidetector CT unique in this diagnostic field, as identification of the neck of the UD is almost impossible with other imaging techniques.<sup>41</sup> Moreover, it is associated to good patient compliance, minimal organ injury and less discomfort compared with traditional UC. Lee *et al.*, in 2014, described the clinical usefulness of CT-VCUG using a 16- multidetector CT in pre-operative evaluation of female UD. In this study, authors reported an exceptional result on 14 consecutive patients who underwent urethral diverticulectomy and were previously studied using the CT-VCUG technique: diverticular ostium was detected by CT-VCUG in all the considered cases, while only in 71.4% by UC.<sup>41</sup> However, some difficulties still need to be overcome to achieve real diffusion in the practice of this imaging technique. In fact, the procedure is time-consuming and voiding while lying on the CT table may be not easy for some patients, thereby lengthening the timing of exam or making the evaluation impossible to obtain adequate voiding images;<sup>21</sup> nevertheless, this last limitation is identical for conventional VCUG. Finally, the problem of radiation should be considered for the patients in reproductive age (the genitalia are within the scan regions).

## Recent findings

In the last years, the international literature focused different aspects of the topic. First of all, more attention has been placed on the diagnostic aspects of videourodynamics (VUDS), known to be useful in 62-95% of patients with UD and also providing additional information on associated urinary disfunction.<sup>42</sup> In a retrospective case note review of 20 women with symptomatic UD, VUDS was diagnostic in 90% (n=18) of UD patients, being helpful in accurately characterizing the symptoms. In 15% of cases, stress urinary incontinence was associated; high detrusor pressure at maximum flow rate and low catheter-free uroflow rate, which indicated the possibilities of bladder outlet obstruction, were observed (40% of

cases).<sup>42</sup> The relevant role of TLUS was confirmed by data from a large retrospective study on 4121 women, examined with 3D/4D TLUS and urethroscopy with a 0-degree cystoscope.<sup>43</sup> In 25 cases (0.6%) were found a major urethral abnormality on TLUS and in 17 case the cystic structure it has been hypothesized to be an UD: urethroscopy confirmed the diverticulum in 16 cases (94%).<sup>43</sup> In 2017, Zhao *et al.* published data on the use of the 640-Multislice CT (640-MSCT), with 3D and 4D reconstruction, to ascertain the existence of the UDs and to figure out their locations, sizes, ostia and shapes in 16 female patients.<sup>44</sup> Using new-generation 640-MSCT, images of a contrast agent-filled urethra during patient voiding were obtained in approximately 5 seconds, providing more detailed urethral structure, which made it possible to identify the UD ostia easily and clearly; also, the high resolution of the system made it feasible to detect the small amount of contrasts passing through the ostia, even the narrow ones. Finally, with the help of post processing techniques, authors reformatted 3D and 4D images, and all patients were diagnosed accurately pre-operation, with a positive predictive values of 100% in diagnosis of female UD.<sup>44</sup> Highly interesting was the recent rare case of a large UD complicating pregnancy in third trimester, influencing the mode of delivery, performed by cesarean section.<sup>45</sup> In fact, the diagnosis and management of UD in pregnancy are challenging because of the rare nature of the condition, the varied presentations and the possibility of misdiagnosis, often related to absence of pelvic examination during second and third trimester. However, early identification of UD during pregnancy may allow for possible aspiration and trial of labor with the anticipation of a vaginal delivery. A notable review of English and Japanese literature on the problem of urethral diverticulum carcinoma (UDC) in women, an extremely rare condition (only 126 reported cases) with several diagnostic difficulties because of its nonspecific presentation.<sup>46</sup> Urine cytology may be a useful initial screening test and has been reported to be positive in 10/11 (91%) cases in which it was utilised. The gold standard investigations to date seems to be a combination of gadolinium-enhanced MRI which can be used for diagnosis, staging and surveillance followed by transvaginal trucut or transurethral biopsies for definitive diagnosis. Moreover, cystoscopy may play an important role in the pathological diagnosis and in localization of the tumor origin and CT may be used to assess for lymph node enlargement, distant tissue and bone metastasis.<sup>46</sup>

## Conclusions

UD is still difficult to diagnose and certainly, the first essential step for a timely diagnosis is the *idea* of the possibility of a UD in women with persistent lower urinary tract symptoms. Clinicians should know the main imaging features of this pathology and also the multiple, currently available techniques for its correct diagnosis. The key point of successful surgical management of UD is correct identification of the ostium.

Current literature data confirm a *resized* role of conventional VCUG alone in the diagnosis of UD. It is not always sufficient for the detection of diverticula and the ostia, and is considered a highly invasive technique. However, it should be remembered that video-urodynamic could be useful in the case of coexistent functional abnormalities, such as incontinence or obstruction. A similar comment can be made for DBU, which has been introduced to improve sensitivity, but the question of invasiveness remains. TL-US is the new favored tool thanks to its minimal invasiveness and easy retrieval, but it still has poor specificity in differentiation from other peri-urethral lesions; consequently, implementation with UC is often needed. It is relevant to also consider that UC has many limitations (such as the definition of diverticular mass features), and moreover it sometimes fails, especially in the difficult case when infection or obstruction is present in the neck of a diverticulum.

Today, MRI and CT-VCUG appear to be the most efficient techniques in the diagnosis and pre-operative definition of female UD. MRI is superior to other techniques in its sensitivity and in showing the relationship between UD and urethral canal, thanks to the multiplane scan and good soft-tissue contrast, but often it does not show the exact location of the ostium. The innovation of 3D-MR sequences and the endorectal coil have improved the traditional results of MRI: the long scanning time has been reduced and the resolution increased. Certainly, the high cost of MRI and its technical accessories remain the main limitation and not all centers have MRI availability.

The use of CT-VCUG (and virtual urethroscopy), while having the classic disadvantage of the conventional contrast enhanced radiologic procedures, represent a very reliable approach providing structural information of the UD, giving both urethral and extraluminal high quality anatomic information. Moreover, it is associated to good patient compliance and minimal organ injury. However, the priority element in these rare cases of UD is above all to suspect the possibility of the pathology in the presence of

significant lower urinary tract symptoms in a woman, in order to get a prompt diagnosis.

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