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ENDOMETRIOSIS AND THE URETER: AN ENDOUROLOGICAL AND GYNECOLOGICAL RISK ASSESSMENT FOR PROTECTION OF THE URETERS.

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ABSTRACT

We present a system for the risk-assessment of uretric involvement in deep-infiltrating edometriosis. The details of 3 patients are discussed. The pre-operative assessments, intra-operative gynecological findings and treatment and post-operative urological follow-up are used to illustrate the specific considerations required to optimize the urological management of deep-infiltrating edometriosis.

Endometriosis is a common condition, predominantly affecting women in their reproductive years. It is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction.[1,2] Endometriosis can vary both in location and severity and is described as 'deep' or 'deeply infiltrating' when it is located in the retroperitoneal space[3] or when it extends more than 5 mm beneath the peritoneum.[4]

It has been long established that severe endometriosis can compromise ureteric drainage and lead to loss of kidney function.[5] Furthermore, endometriosis is an established risk factor for sustaining an iatrogenic ureteric injury during gynecological surgery. Recent data from the British Society for Gynecological Endoscopy endometriosis centres found a 0.5% ureteric complication rate for cases of rectovaginal endometriosis.[6] This suggests improvement in the risk from a previous report published in 2012, in which Park et al documented an overall 1.1% risk of ureteric injury in laparoscopic cases and 1.2% in laparotomy cases based on a retrospective review of 2,927 patients.[7] Importantly in this study, patients with risk factors (endometriosis, pelvic inflammatory disease, previous pelvic surgery, a prior history of pelvic radiation and patients with congenital anomalies) had a 2.7 % risk of ureteric injury compared to a risk of 0.9% in those without these risk factors.[7]

Whilst endometriosis has classical presenting symptoms, with dysmenorrhea in 81%, non-cyclical pelvic pain in 70% and dyspareunia in 66%, most patients have no urological symptoms, even in cases with ureteric involvement. Fortunately, when the ureter is affected, it can be detected by upper tract imaging: Cavaco-Gomes et al have reported prior hydroureter/hydronephrosis in 48% patients who were shown to have endometriosis affecting one or both ureters at the time of their gynecological surgery. In their systematic review of 18 articles (analyzing data from 700 patients) the left ureter was affected slightly more frequently than the right (in 54% of cases) was bilateral in 11% of patients and additionally involved the bladder in 20% of patients. Over half of these patients had significant posterior compartment disease (either rectovaginal or uterosacral involvement). When these patients underwent gynecological treatment, ureterolysis was sufficient in the overwhelming majority (87% of patients) with reconstructive ureteric surgery required in the remaining 13%.[8]

Gennaro et al have shown similar findings in a retrospective analysis of 386 women undergoing complex endometriosis surgery, whereby 82% were managed by ureterolysis alone, with 18% needing urologic surgical expertise (including ureteric stent insertion, or more invasive interventions such as a more extensive ureteric dissection with an omental wrap, or even ureteric re-implantation). They found that patients with prior flank pain, any urinary symptom or hydronephrosis on pre-operative imaging were significantly more likely to require major urological intervention.[9]

NICE guidance on endometriosis recommends that women with severe endometriosis are treated in centres within a multidisciplinary set-up[9] including gynecologists, colorectal surgeons and urologists. As far as the urological involvement is concerned, the goal is to protect long-term renal function and facilitate the excision of endometriosis whilst minimizing the need for ureteric re-implantation.

We present the details of 3 patients who were referred to our endometriosis centre for multidisciplinary care with deep infiltrating endometriosis. The pre-operative assessments, intra-operative gynecological findings and treatment and post-operative urological follow-up are discussed to illustrate the specific considerations required to optimize their urological management.

Case 1 was a 29-year old lady with an established diagnosis of endometriosis in whom left sided ureteric involvement was identified by MRI. A narrow segment was demonstrated in the lower third of the left ureter at ureteroscopy with a dilated ureter above (Figure 1A).

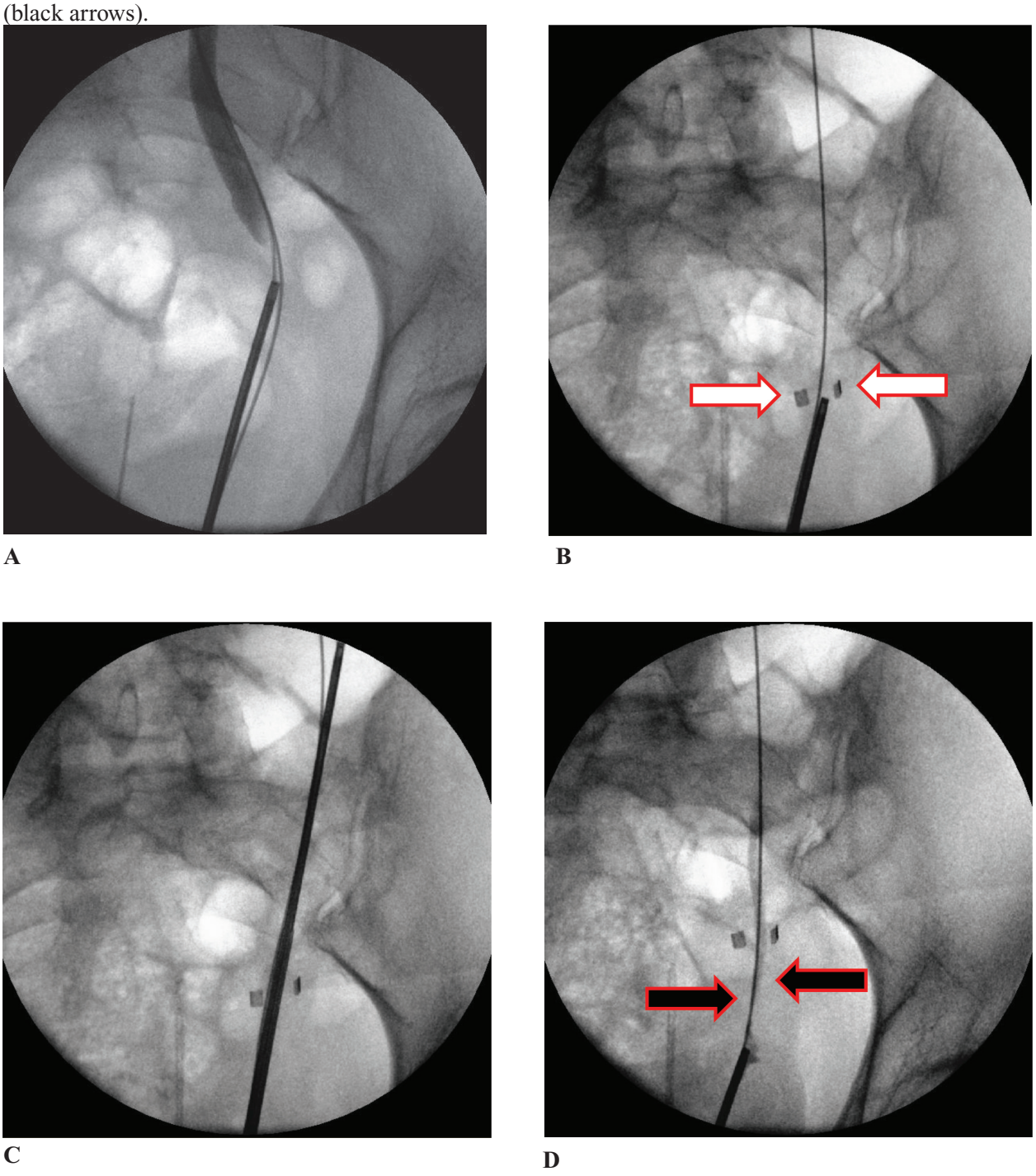
Following hormone therapy with LHRH analogues, the definitive gynecological treatment was achieved by laparoscopy, which revealed left pelvic side wall disease and a rectovaginal nodule; the latter was excised with shaving the surface of the left ureter. A repeat ureteroscopy 6 weeks post-operatively showed an improved lumen, such that the ureteroscope could be advanced beyond the site of the previous narrow segment to the proximal ureter (Figure 1B and 1C). Contrast drained across this, suggesting no residual obstruction (Figure 1D), which was confirmed with a subsequent MAG3 renogram (Figure 2).

Case 2 was a 39-year old lady who pre-sented with left sided pain, investigated by CTKUB for suspected ureteric colic, which demonstrated a left sided hydronephrosis and hydroureter. A pelvic MRI showed deep endometriosis involving the rectovaginal space. A left sided ureteroscopy was performed prior to laparoscopic endometriosis treatment, which showed a dilated ureter with an obvious caliber change at the level of a stricture in the lower third of the ureter (Figure 3A); this was optically dilated by advancement of the scope to the renal pelvis, and a 6Fr JJ stent inserted, with an additional right sided stent for ureteric identification. Laparoscopy revealed a right sided endometrioma, a significant left utero-sacral nodule overlying the ureter (see Figure 3B) and a large utero-vesical nodule. This was treated by excision of the utero-vesical nodule, with shaving of the endometriosis involving the surface of the bowel and the left ureter, freeing this with both sharp and blunt dissection from the surrounding fibrosis. A urethral catheter was left on free drainage for 3 weeks, at which stage a cystogram demonstrated no leak, with contrast reflux up both ureters (Figure 4A and B). Her JJ stents were removed under local anaesthetic 3 weeks later, with a follow-up MAG3 demonstrating preserved renal function with a dilated but unobstructed picture (Figure 4C).

Case 3 was a 35-year-old lady with pre-vious endometriosis who presented with recurrent symptoms including lower urinary tract symptoms and bladder pain. An MRI confirmed rectovaginal endometriosis and also identified bilateral endometriomas and bilateral hydronephrosis, more noticeably on the left side. LHRH analogues were started, and a left sided ureteroscopy was performed to negotiate a tight stricture in the lower third of the ureter with a tortuous, dilated ureter above (Figure 5A–D). Given the anticipated extent and severity of her disease, a contralateral right sided stent was inserted to aid intra-operative ureteric identification on that side.

A two-stage approach was required to treat her endometriosis. At the first stage, a rectovaginal nodule was identified on the left side, with adherent bowel and fibrosis around the left lower ureter. Bilateral endometriomas (3 cm on the right and 8 cm on the

FIG. 1 Narrow segment in the lower third of the left ureter in case 1 with dilatation above. The ureter shows angulation due it being fixed at this point secondary to endometriosis at that position. At the second look procedure, the ureter has a more normal course and wider lumen, as demonstrated by Figure 1B and 1C, whereby the ureteroscope has been advanced beyond the previously narrow segment to the proximal ureter. Surgical clips from the intervening laparoscopy are shown with white arrows at the position of the previous stenosis. Figure 1D shows contrast in the ureter, and that this is no longer dilated (black arrows).



A **B**

C **D**

FIG. 2 Post-operative MAG3 renogram for case 1, demonstrating normal uptake, renal handling and drainage phases for both kidneys. This confirmed that the Left kidney had normal split function, and undilated, unobstructed drainage.

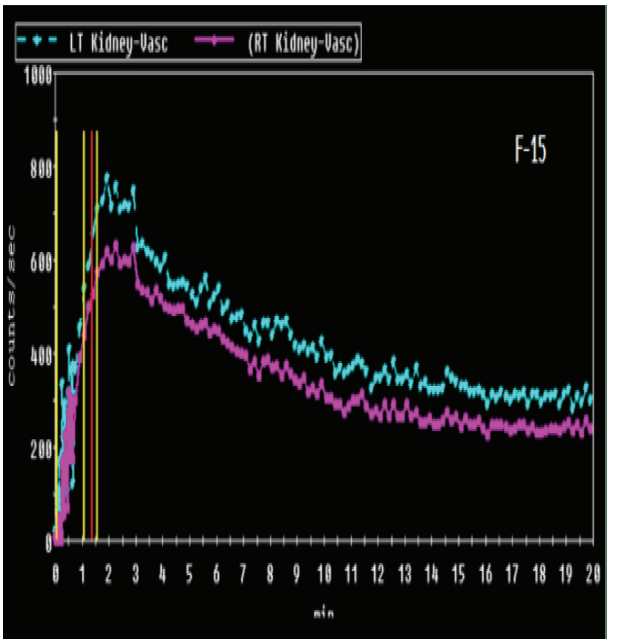
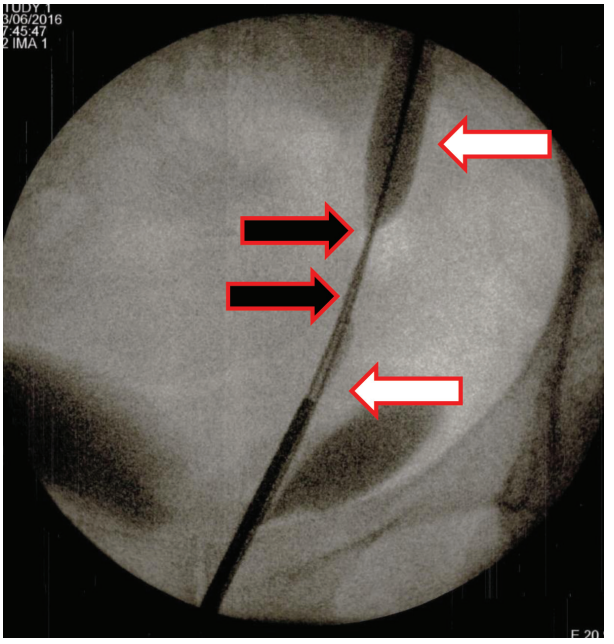
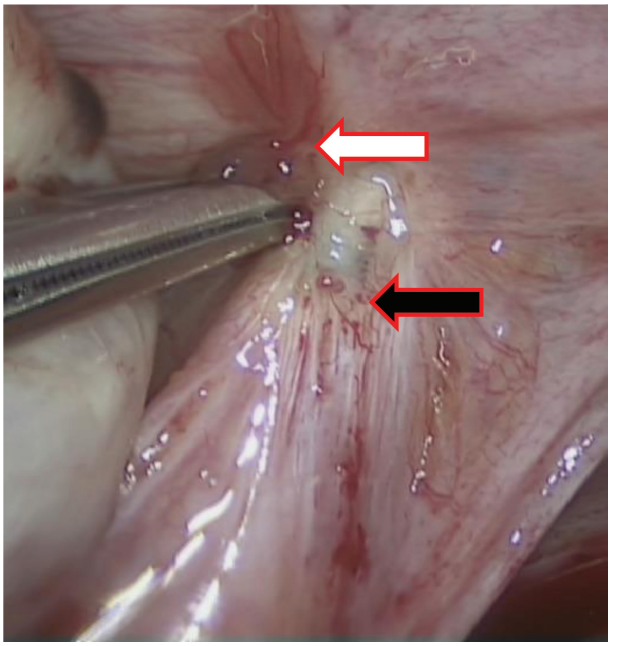


FIG. 3A This demonstrates an obvious calibre change from dilated ureter above to a more normal calibre below (white arrows) with an intervening stricture (black arrows) secondary to a left sided uretero-sacral nodule of endometriosis. This nodule can be seen in **FIG. 3B** (white arrow) with the ureter (and stent) also visible (black arrow).

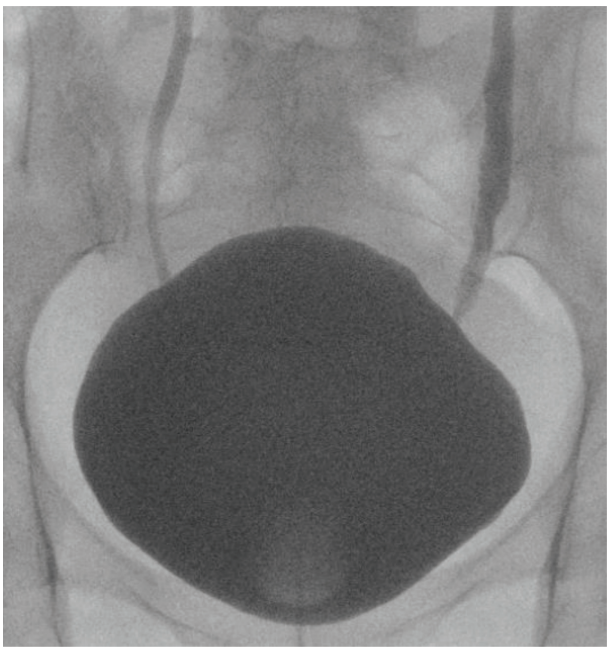


A



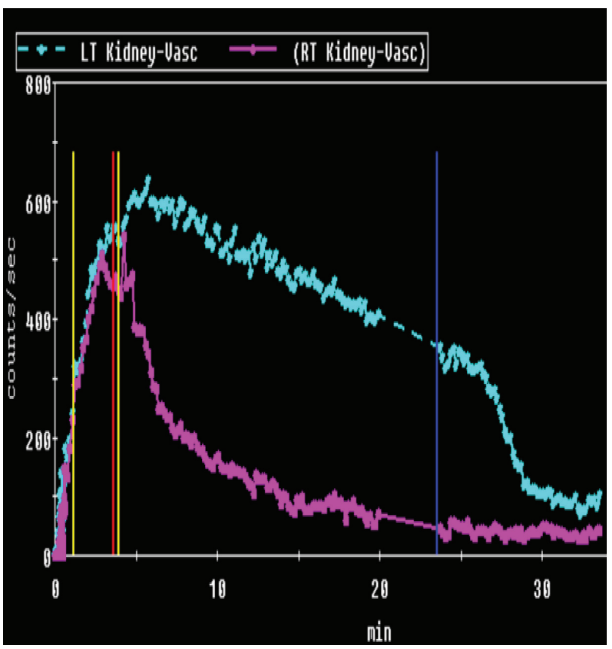
B

FIG. 4A and FIG. 4B Shows the post-operative cystogram for case 2, confirming water-tight healing from the excision of the vesical nodule of endometriosis. The images also demonstrate free reflux of contrast up both ureters, and that the calibre of the left ureter now looks more normal. After removal of the JJ stents, a subsequent MAG3 renogram showed normal uptake of the radioisotope by both kidneys, with the left having a dilated but unobstructed drainage pattern **FIG. 4C**.



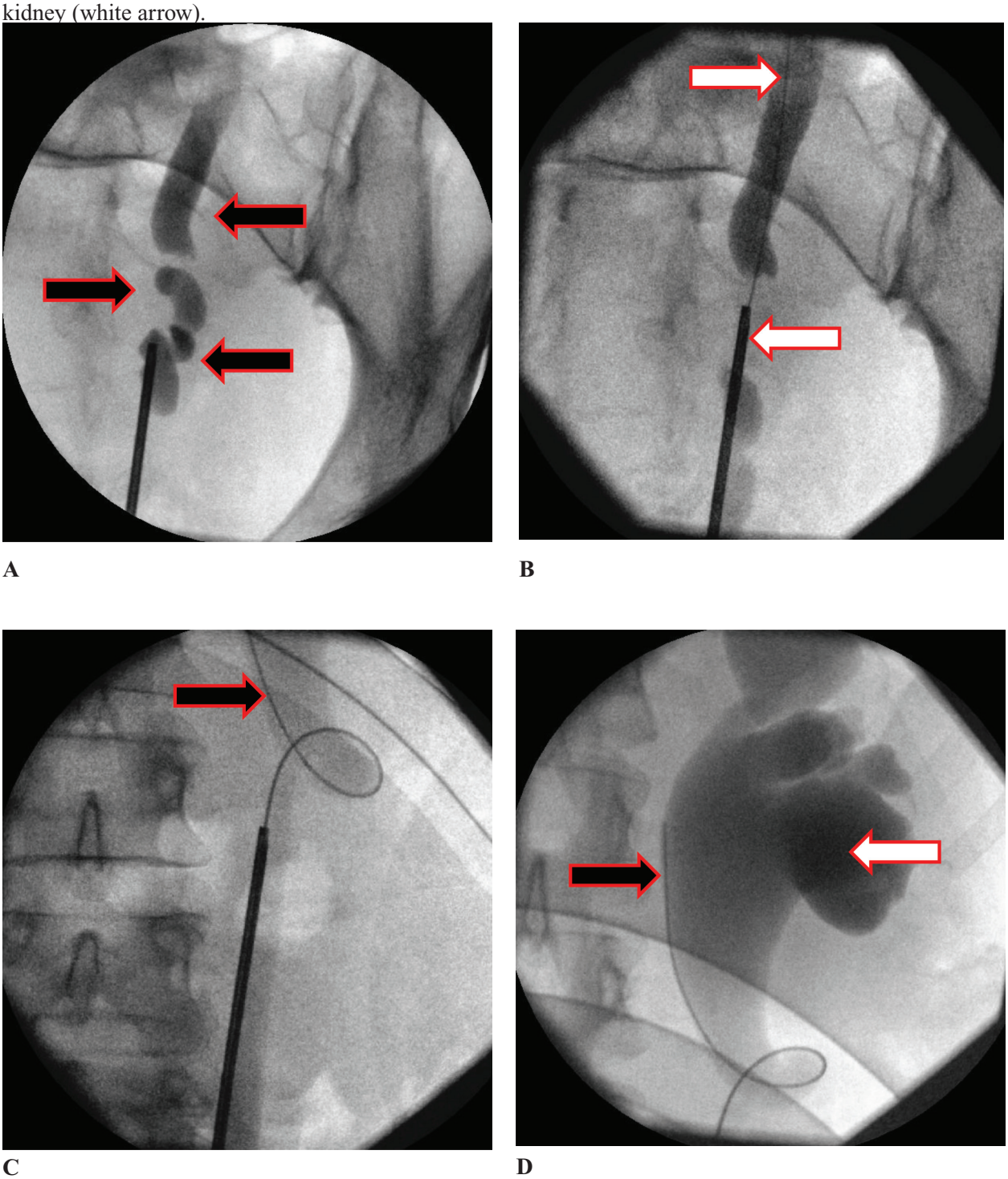
A

B



C

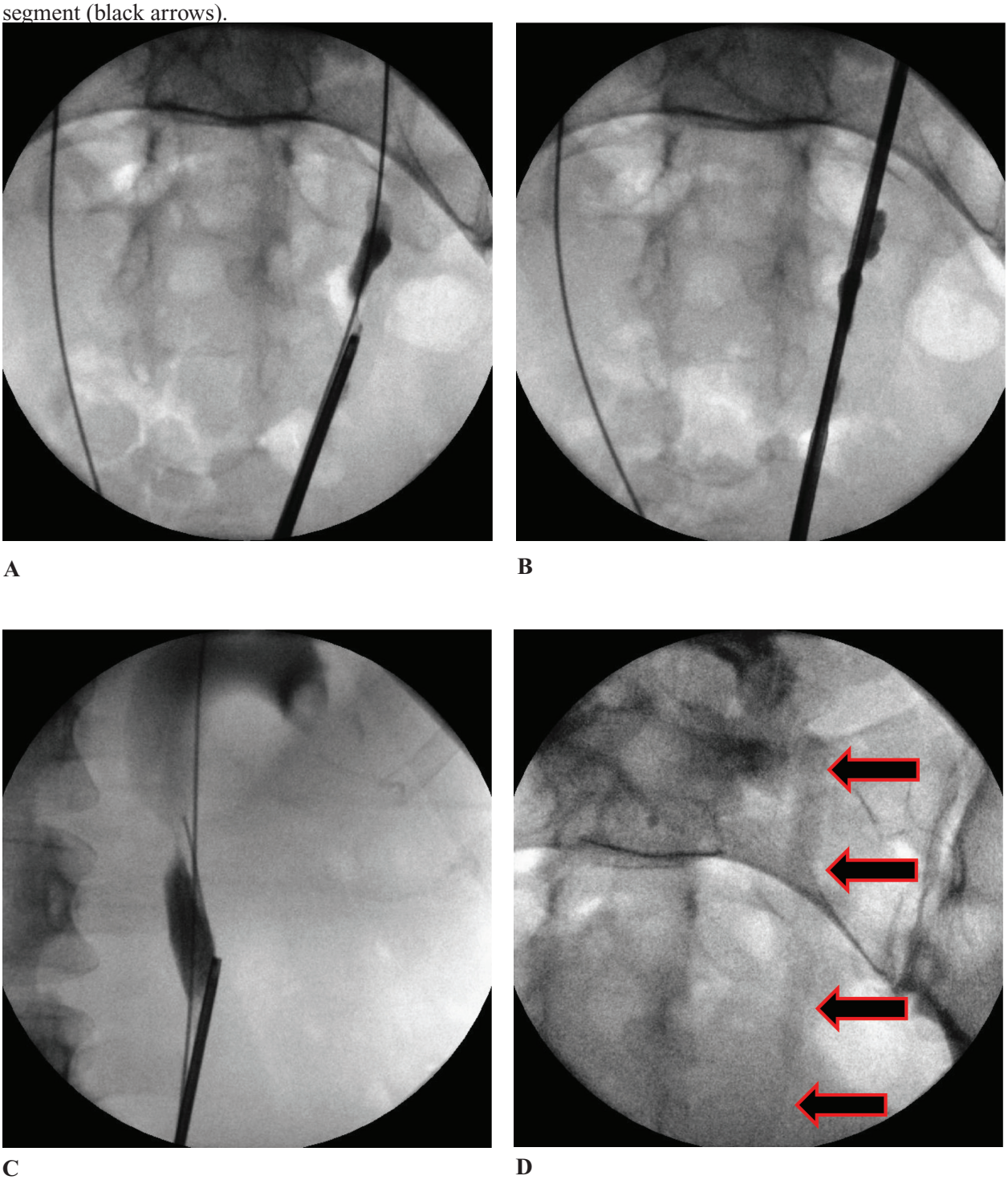
FIG. 5A and FIG. 5B show the dilated, tortuous lower ureter (black arrows) of case 3, requiring gradual advancement of the ureteroscope and working guide wire (white arrows) towards the proximal ureter. **FIG. 5C and FIG. 5D** show the effect of longstanding dilatation of the upper ureter with a "loop-the-loop" effect as the working wire (black arrow) was advanced to the hydronephrotic kidney (white arrow).



A **B**

C **D**

FIG. 6A–6C The left ureter of case 3 now has a more straightforward course following her two-staged endometriosis treatment, allowing the ureteroscope to be advanced to the proximal ureter more easily than at the initial procedure demonstrated in **FIG. 6A–D.** A safety wire can also be seen in the right ureter in **FIG. 6A and FIG 6B. FIG 6D** shows faint contrast draining across the previous strictured segment (black arrows).



A **B**

C **D**

left) were drained. At the second stage, after further LHRH therapy, the ureters were dissected and the rectovaginal endometriosis was excised, requiring shaving the nodule off the surface of the bowel and around the left ureter. The left fallopian tube and ovary were removed. The JJ stents were changed at the end of the procedure. A re-look ureteroscopy was performed 12 weeks after the completion of the gynecological surgery, at which the ureteric anatomy was much more favourable, particularly on the left side (Figure 6A–D). Although the left ureter was still somewhat narrow, contrast drained adequately such that both JJ stents were removed. A follow-up MAG3 renogram 3 weeks later demonstrated the relative function of her left kidney had been maintained, and showed unobstructed drainage, having been clearly obstructed before the initial ureteroscopy and stent insertion (Figure 7A and B).

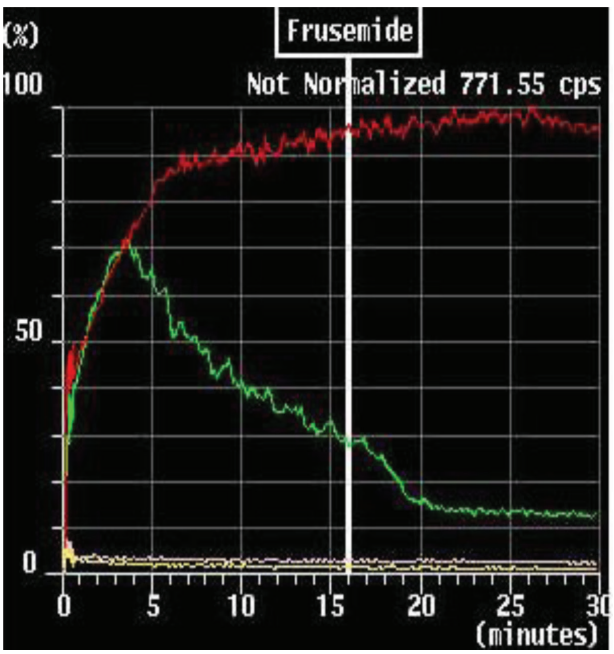
DISCUSSION

In order to help judge the likelihood of needing urological involvement in the management of their endometriosis, we have devised a scoring system (see Table 1) for patients undergoing rectovaginal deep endometriosis surgery based on specific pre and interoperative risk assessments. Values are recorded for pre-operative presentation, appearances at surgery, post-operative urological assessment and follow-up findings. Each patient is allocated a score based on the highest level of risk within each category, ranging from zero, representing no concern for that category, to a maximum of 5 points.

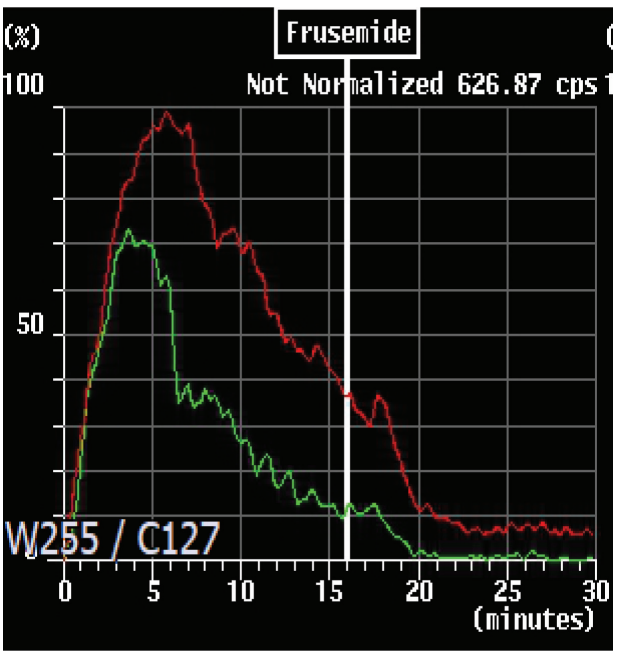
Pre-operative Assessment

In addition to the documentation of the patient's gynecological symptoms (dysmenorrhea, dyspareunia and dyschezia), details of previous surgery should be

FIG. 7A and FIG 7B "Before and after" MAG3 renograms for case 3. **FIG. 7A** shows a classical obstructed curve, where there is no drainage from the left kidney (represented by the red line), including after Frusemide challenge (at the vertical white line at 15 minutes). After treatment, the renogram curve for the left kidney (again represented by the red line) in **FIG. 7B** shows that its relative function has been maintained during her treatment, and now has a clearly unobstructed drainage pattern.



A



B

TABLE 1 Pre-operative, Intra-operative and Follow-Up Risk Factors for Urological Sequalae in Deep Infiltrating Endometriosis

SCORE	Pre-operative	Intra-operative Gynecological	Early Post-operative EndoUrological	Longer Term Post-operative Follow-Up
0	No concerns	No urological involvement	None required (including JJ stent removal under local anaesthetic)	MAG3 not needed or normal (equal function, unobstructed)
1	Previous surgery involving ureteric dissection	Peri-ureteric endometriosis / tethering	Normal appearances	MAG3 reduced function BUT unobstructed (relative contribution 43% or less)
2	Loin pain	Pollack inserted (immediately pre-op or during operation)	Fixed ureter (normal lumen) Contrast draining	MAG3 obstructed (But function greater than 25%)
3	Hydronephrosis	JJ stent inserted (either pre-operatively or intra-operatively)	Narrow lumen Contrast draining	MAG3 reduced function (25% or less) AND / OR obstructed
4	JJ stent in situ	Ureteric breach (requiring suture repair to close defect)	Fixed AND Narrow ureter Contrast draining	Post-operative nephrostomy required
5	Loss of function on renography (MAG3 or DMSA)	Ureteric transection (requiring end-to-end anastomosis or re-implantation)	Obstructed ureter No contrast draining Re-stented	Urological reconstruction required

recorded. Patients who have had previous extensive pelvic surgery are at established risk for ureteric injury at future surgery, and therefore score one point on the pre-operative scale.

Additional symptomatic enquiry should include bowel and bladder function, with specific questions regarding the occurrence of loin pain, which raises the possibility of ureteric obstruction, and should trigger a renal tract ultrasound as the next step. A KUB (Kidney Ureter and Bladder) ultrasound should also be performed if patients have an abnormal serum creatinine and eGFR. Finally, patients with known, severe endometriosis should have a renal tract ultrasound regardless of loin pain or blood test results, to exclude "silent obstruction" (i.e., asymptomatic upper tract dilatation secondary to gradual ureteric obstruction, in whom the serum creatinine and eGFR may not change in the presence of a normal contralateral kidney).[11] Loin pain with normal imaging scores 2 points in this domain, and 3 points if hydronephrosis is confirmed on imaging.

The identification of hydronephrosis should lead to a urological referral to consider pre-operative ureteric drainage with a JJ stent, both to protect the function of the affected kidney, and to aid intra-operative ureteric identification, scoring 4 points in the pre-operative domain. In these circumstances, given the anticipation of a more complex gynecological dissection, further

anatomical information regarding the proximity of endometriosis in relation to the ureter may be obtained from a more detailed ultrasound scan or more commonly a pelvic MRI.

Finally, pre-operative isotope renography by MAG3 (to confirm / refute obstruction and/or loss of function in the context of hydronephrosis) is a useful in patients in whom hydronephrosis has been identified. If the MAG3 is reassuring, no active urological intervention will be needed prior to surgery (although JJ stents may be inserted intra-operatively; see below). However, if there is obstruction or loss of function, pre-operative drainage of the affected kidney would be recommended either by JJ stent or nephrostomy insertion to avoid any further loss of function whilst awaiting endometriosis surgery. Patients with established loss of function on MAG3 score 5 points in the pre-operative column.

Intra-operative Gynecological Assessment

Whilst the pre-operative assessment will inform the gynecologist of the potential for intra-operative urological issues, a precise intra-operative assessment of the location, nature and extent of endometriosis is essential, particularly for areas that may not have been detected by pre-operative imaging. This is certainly true in relation to the ureter, where the nature of the gynecological dissection may have an impact on the patient's post-operative care and protection of renal function. Endometriosis deposits in close proximity to the ureters should therefore be mapped and documented, and the degree of fibrosis or tethering noted. In this domain, a score of zero indicates no urological involvement, whilst endometriosis in close proximity to the ureter, or causing tethering, and therefore requiring some ureteric dissection scores one point. A temporary ureteric catheter can be a useful aid to identify the ureter and may be required where ureteric dissection and identification is more challenging. Thus, inserting one can be considered a marker of more challenging surgery and therefore of increased risk, and scores 2 points in this column.

In extensive peri-ureteric endometriosis or fibrosis, a more extensive dissection and ureterolysis to "strip" the surface of the ureter will be needed, which further increases the potential for ureteric compromise. In such cases, post-operative drainage with an indwelling stent is preferable to a temporary ureteric catheter, and scores 3 points. This score is recorded regardless of whether the stent has been inserted pre-operatively (i.e. for hydronephrosis) or intra-operatively (as a result of the need for extensive ureteric dissection).

Where actual damage has occurred to the ureter, either inevitable (due to the extent of the disease) or accidental (i.e. surgical misadventure, such as suture or diathermy injury, partial laceration or complete transection) the findings must be recorded, and managed as appropriate. This ranges from an intra-operative JJ stent insertion in cases without one already, through to a simple suture repair of a small ureteric defect to more major urological reconstructions (spatulated end-to-end ureteric anastomosis or ureteric re-implantation with either a psoas hitch or Boari flap reconstruction). Fortunately, intra-operative ureteric surgery such as this is rare, but represents a further risk for post-operative ureteric compromise, and is accordingly scored increasingly highly on the risk evaluation chart, with 4 points for closing a ureteric defect and 5 points for a ureteric anastomosis or re-implantation.

Post-operative Assessment

There are 2 aspects for consideration in relation to post-operative assessment: the short term, in the form of post-operative complications and the intermediate term by the radiological and/or endourological assessment of the ureter in relation to its appearance and drainage.

Short Term Assessment

Patients with unidentified intra-operative ureteric damage will present in the post-operative period with either loin pain, a rising serum creatinine / reducing eGFR, or excess output from an abdominal drain, or a combination of these. Whilst a renal tract ultrasound offers information about hydronephrosis, the most useful test in these circumstances is a contrast enhanced CT, including a delayed phase "urographic" sequence. This will identify obstruction, dilatation and, if present, ureteric leak. Depending on the findings, particularly whether there is obstruction or leak, a JJ

stent or nephrostomy will be the likely initial "recovery" step. Of these, a nephrostomy provides the most straightforward and reliable drainage (at the expense of the inconvenience of an external drain) and a route for a subsequent antegrade stent or "rendezvous" procedure.[12] In rare cases, a laparotomy and early ureteric reconstruction may be required.

Planned Ureteric Reassessment

If there have been no pre-, intra- nor post-operative urological complications, then scheduled post-operative ureteric assessment is not necessary, and the patient can be considered low-risk, with a score of zero recorded in the Endourology review column. This score applies to patients who have had no ureteric involvement with endometriosis and those with a temporary ureteric catheter during the intra-operative period which has been removed at the end of the procedure. Patients who have a JJ stent in situ must be followed to avoid problems with prolonged stent-related bother or stent encrustation. Most importantly, the stent must either be removed or changed, a decision that requires assessment of the prior complexity of the patient's endometriosis, and of the likelihood that the ureter has maintained a favourable lumen for drainage. A score of zero can also apply to patients who had a JJ stent (or stents) inserted but which are simply removed without imaging or ureteroscopic assessment. In cases where the ureter needs further assessment, a retrograde study to judge the ureteric calibre and drainage, or ureteroscopy, which adds information about the "look and feel" of the ureteric lumen (i.e. whether the lumen appears tight or tethered due to mural or external fibrosis respectively). Both retrograde studies and ureteroscopy offer the opportunity to insert a fresh JJ stent if the appearances are unfavourable.

The decision that ureteric assessment by retrograde studies or ureteroscopy is needed, even if shown to be reassuring, reflects a degree of post-operative concern, and places the patient in a slightly higher risk group than simply removing the stents, and scores one point in this domain. The next 3 levels of risk relate to degrees of ureteric abnormality, but with adequate drainage of contrast such that a JJ stent is not re-inserted. At the lower end of concern, scoring 2 points on the scale, is the finding of a "fixed" ureter secondary to external fibrosis from the surgery, making advancement of a ureteroscope difficult, but with a good lumen which drains contrast feely. The next level is a narrow segment of ureteric lumen due to mural fibrosis (scoring 3 points), through to both a "fixed" and narrow ureter (scoring 4 points). The identification of an obstructed ureter requiring re-insertion of a JJ stent represents the greatest risk to future renal compromise and therefore scores 5 points.

Longer Term Urological Follow-up

In terms of longer term post-operative surveillance, patients without pre- or intra-operative urological involvement are unlikely to need any urological follow-up. Those who have had largely straightforward peri-operative course may benefit from a KUB ultrasound as part of their follow-up to exclude dilatation of the collecting system suggestive of silent obstruction. If this is normal, these patients can also be discharged from urological follow-up. Patients who have had pre-operative, intra-operative or post-operative ureteric involvement need early post-operative urological review including post-operative imaging when the ureter has been rendered stent free. This is best achieved by MAG3 renography for the relative contribution of the kidney and its drainage pattern to confirm whether the ureter has healed without loss of function, and that the drainage of the kidney is unimpeded by the formation of a stricture. If the MAG3 is normal (or not required at all) then the patient is at the lowest level of risk, scoring zero points for the post-operative domain.

The next levels of risk relate to loss of function according to the MAG3 curves with one point for loss of function without obstruction (i.e., below the reference level for an acceptable relative function of 43%), and 2 points for similar loss of relative function but with a rising, obstructed curve. More serious loss of function (to less than 25% of the overall renal reserve) affords a score of 3 points.

Any abnormality of drainage according to MAG3 or urological ureteric reassessment that needs re-intervention by JJ stent / nephrostomy represents not only loss of function but a likely ureteric stricture,

and scores 4 points in the post-operative urological drainage domain. Those patients who have a stricture confirmed, and proceed to ureteric reconstruction score a maximum 5 points in this column.

The point scoring described in the text for each category has been summarized in Table 1.

CONCLUSIONS

Ultimately, the purpose of urological involvement in patients with endometriosis is to avoid progressive or untreated loss of renal function. In this regard, it is important for both gynecologists and urologists to be aware that, even in deep infiltrating endometriosis, most patients are asymptomatic from the urological perspective, and particularly so for the upper tract. However, nearly half of patients with ureteric endometriosis will have hydronephrosis on imaging, and therefore including an ultrasound of the kidneys in the initial assessment of patients with endometriosis is good practice.

Endometriosis patients who have loin pain or hydrodronephrosis at presentation are at risk of needing intra-operative urological input. Such patients should be referred to a Urologist to allow decisions regarding JJ stent insertion to be made prior to their gynecological surgery. This may be performed as an initial separate step (represented by case 1 and case 3 above) or as part of a combined procedure (as performed in case 2 above).

As with all complex conditions, collaborative multidisciplinary working is likely to achieve the best results for these patients. We hope that the 3 cases have illustrated the pre-operative, intra-operative and post-operative factors to consider in treatment planning, and that our assessment table will alert clinicians to risk factors for ureteric compromise and help avoid the silent loss of renal function. On the other hand, in the context of scarce resources, we recognize that it is equally important to stratify care to identify low-risk patients who can be safely discharged. As such, we aim to evaluate the scoring system to ascertain whether it could be used to predict the final urological outcome, and therefore aid counselling patients as to the likely outcome they should expect from their endometriosis treatment.

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