

PREOPERATIVE PREDICTION OF URETERAL ENDOMETRIOSIS WITHOUT
DILATATION: INSTRUCTIONS FOR USE

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There is a major difference in the clinical presentation of endometriosis causing intestinal or ureteral stenosis. Whereas a severe bowel stricture originating from endometriosis infiltration by definition gives rise to subocclusive symptoms, obstructive uropathy due to ureteral endometriosis may go unnoticed and cause progressive hydronephrosis in the absence of colicky pain (1, 2).

Women with a diagnosis of deep endometriosis, which is the lesion phenotype most frequently associated with ureteral involvement, should systematically undergo an ultrasound evaluation of the urinary tract to rule out ureteral dilatation. Although infrequently, a reduced or absent kidney function can be detected with elusive or no previous suggestive symptoms (1, 2). Awareness of this potential condition, ultrasonographic screening, and active surveillance of all women with deep endometriotic lesions, might limit the risk of this severe disease complication.

Now Arena and co-workers (3) try to take a further step forward, that is, predict ureteral involvement owing to extrinsic compression or distortion caused by endometriosis even in the absence of stenosis and secondary ureteral dilatation. To this aim, they prospectively assessed a series of women with a diagnosis of deep endometriosis of the posterior compartment scheduled for excisional surgery. In addition to detailed clinical evaluation, including the use of validated scales for measuring symptoms severity, the patients systematically underwent transvaginal and transabdominal ultrasonography. According to the authors, *“the diagnosis of ureteral involvement required the retroperitoneal isolation and examination of the diameter, course, and consistency of both ureters in the pelvis”*. During a 40-month period, 300 consecutive patients underwent surgery for posterior deep infiltrating endometriosis (DIE), and ureteral endometriosis was diagnosed in 145 of them (48.3%). After exclusion from the analysis of the 16 women with a pre-operative hydronephrosis diagnosis, non-obstructive ureteral endometriosis was associated with previous surgery, a posterior nodule with a transverse diameter of over 1.8 cm, parametrial involvement, and adenomyosis.

Some methodological and clinical considerations might help contextualize the study findings into everyday practice.

The diagnostic standards adopted seem somewhat undefined. Ureteral dilatation is a fact whereas, in the absence of hydroureteronephrosis, any other non-objectively measurable criterion inevitably introduces a variable degree of subjectivity. The authors argue that in all cases endometriosis has been histologically demonstrated in lesions adjacent to the ureter and removed during ureterolysis. This is reassuring, but still may not ensure adequate reproducibility of the diagnosis, and what would have been the inter-observer variability had the same women been operated on by other surgeons is uncertain.

Moreover, in this series, the positive and negative predictive values of the test were 66% and 72%, respectively. Considering the high prevalence of the condition (about 50%) these values probably did not markedly change the surgical approach. Of relevance, the prevalence of the index condition influences the predictive values: if the prevalence of the ureteral endometriosis decreases, the positive predictive value also tends to decrease (for example to about 40% in case of a prevalence of 25%), but the negative predictive value should increase (and vice versa in case of higher prevalence). These considerations underline the fact that the result of the “test” should be considered cautiously when planning surgical procedures, especially in hospitals with different ureteral endometriosis prevalence rates.

In addition, the high prevalence of ureteral endometriosis could indicate *per se* a selection bias, as women with particularly severe conditions might be referred or self-refer to the authors’ renowned and highly valued center of expertise. Again, if this is true, the generalizability of the observed results might be limited.

Indeed, at least three out of the four identified predictors, that is, previous surgery, the transverse diameter of a posterior compartment lesion, and parametrial fibrotic infiltration, should always raise the suspicion of possible ureteral involvement. As an example, the lateral border of a large rectovaginal lesion might be very close to the distal ureteral tract. For similar anatomic

reasons, the risk of ureteral involvement is especially high when endometriotic fibrosis affects the lateral parametria. As the authors themselves clarify, previous surgery might constitute a risk factor because, in case the procedure was not performed in centers of expertise, deep lesions that require particularly high technical capabilities to be safely excised, are frequently left behind. As a result, often women self-refer to these centers only when repeat surgery is eventually necessary. The identification of adenomyosis as a predictor of ureteral endometriosis could be explained by the observed strong association with deep infiltrating endometriosis (4).

According to the authors, their findings are important because 1) “*the suspicion of ureteral involvement is crucial for the correct surgical planning, requiring an expert surgeon*”, 2) “*treatment of early lesions can prevent subsequent ureteral stenosis and potentially the loss of renal function*”, and 3) the correct prediction of the condition allows “*extensive preoperative counseling for patients*”. These seem three fundamental but partly separate principles that merit distinct considerations.

1) When almost one in two women turns out to have ureteral endometriosis, it seems sensible to systematically plan the procedure with an expert surgeon with sufficient training to deal with severe, infiltrating deep lesions wherever they are found and independently from the presence of the identified predictors of ureteral endometriosis. Indeed, all the women in the present series were operated by a single, extremely capable surgeon. In such a setting, correctly predicting non-obstructive ureteral involvement may not change the outcome to a great extent, as women are operated on by the best available surgeon anyway. In other less specialized settings, the prediction of ureteral involvement may well be more relevant but, in our opinion, not so much to try to better plan the surgical team, but instead to refer the patient to centers of expertise with the objective of optimizing the efficacy of the procedure and minimizing the risk of complications, two variables that are strictly operator-dependent (1, 2, 5).

One essential clinical message provided by the authors is that “*routine intraoperative retroperitoneal identification and inspection of both ureters is highly advisable in all women*

undergoing surgery for DIE". This is a very useful safety maneuver not only to identify extrinsic ureteral compression but also to prevent inadvertent and potentially unrecognized intraoperative iatrogenic ureteral lesions. However, not all gynecologists are trained to safely perform ureteral isolation and ureterolysis in women with severe deep endometriosis, even when lesion sites and characteristics are correctly predicted preoperatively (5).

2) It is conceivable that some of the excised infiltrating endometriotic lesions externally compressing or distorting the ureter, if not correctly identified and removed would have progressed and caused stenosis and hydroureteronephrosis in the future. However, this study was not designed to define this outcome, and the value of preoperative identification of ureteral endometriosis without stenosis in preventive terms remains to be determined. Moreover, it would be important to define the needed number of women who should undergo ureterolysis and excision of endometriotic lesions externally compressing the ureter to prevent one case of obstructive uropathy. Of relevance here, also the associated morbidity, especially when the above procedures are not performed by expert surgeons, should be included in the overall balance.

3) All women candidates for excision of deep infiltrating endometriotic lesions of the posterior compartment must always receive complete, evidence-based, balanced, and quantitative information regarding the expected benefits of the proposed procedures, types and percent risk of different complications, including a detailed description of short- and long-term health consequences, and treatment alternatives, independently of lesion diameters or other preoperative predictors of extrinsic ureteral compression without ureteral dilatation. This type of counseling may take time but is of invaluable ethical, psychological, and practical importance. It would be unfortunate if a surgeon who does not care about adding much time at the operating table to pursue radicality in endometriotic lesions excision, would struggle in adding some minutes to the preoperative consultation to empower patients in reaching an adequately informed decision.

In conclusion, the authors should be commended for identifying the above predictors of non-obstructing ureteral endometriosis, as this can translate into augmented awareness of the condition,

optimal selection of surgeons and, hence, a potential increase in the efficacy of the procedure and, most notably, improvement in patient safety. As the most important factor in determining the outcome of surgery for deep endometriotic lesions infiltrating pelvic structures and organs, including the ureter, appears to be the availability of capable gynecologists, abdominal surgeons, and urologists with specific experience in severe endometriosis forms (2), the most profitable use that gynecologists can make of Arena et al.' findings, is probably to refer women to tertiary care centers once deep endometriosis with possible ureteral involvement has been preoperatively predicted. The incremental benefit of being treated in such centers compared with general hospitals could also be studied and measured, as its magnitude might result larger than that attainable with any predictive algorithm when applied in non-specialized hospitals.

REFERENCES

1. Nezhat C, Falik R, McKinney S, King LP. Pathophysiology and management of urinary tract endometriosis. *Nat Rev Urol.* 2017;14:359-372.
2. Barra F, Scala C, Biscaldi E, Vellone VG, Ceccaroni M, Terrone C, Ferrero S. Ureteral endometriosis: a systematic review of epidemiology, pathogenesis, diagnosis, treatment, risk of malignant transformation and fertility. *Hum Reprod Update.* 2018;24:710-730.
3. Arena A, Del Forno S, Orsini B, Iodice R, Degli Esposti E, Aru AC, Manzara F, Lenzi J, Raimondo D, Seracchioli R. Ureteral endometriosis, the hidden enemy: multivariable fractional polynomial approach for evaluation of pre-operative risk factors in the absence of ureteral dilatation. *Fertil Steril* 2021, in press.
4. Marcellin L, Santulli P, Bourdon M, Maignien C, Campin L, Lafay-Pillet MC, Millischer AE, Bordonne C, Borghese B, Dousset B, Chapron C. Focal adenomyosis of the outer myometrium and deep infiltrating endometriosis severity. *Fertil Steril.* 2020;114:818-827.
5. Cunha FLD, Arcoverde FVL, Andres MP, Gomes DC, Bautzer CRD, Abrao MS, Tobias-Machado M. Laparoscopic Treatment of Ureteral Endometriosis: A Systematic Review. *J Minim Invasive Gynecol.* 2021;28:779-787.