

The association of clinical symptoms with deep infiltrating endometriosis: the importance of the preoperative clinical assessment

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Over the last several years, with improvements in laparoscopic surgical techniques, specialized surgical teams have successfully been able to safely excise deep endometriosis lesions that infiltrate into and may compromise the bladder, bowel, ureter and other pelvic regions. Excision of deep infiltrating endometriosis (DIE) lesions warrant special surgical approaches and may necessitate either additional training or a multidisciplinary team of general surgeons and urologists working alongside gynecologists. Lafay Pillet and her colleagues are surgical specialists at a well-recognized referral center of excellence for these challenging endometriosis cases. In their paper included in this issue of the Human Reproduction, they address a key aspect of the surgical management of DIE lesions (Lafay Pillet *et al.*, 2014). Using clinical symptoms, they develop a clinical scoring system which helps to predict the existence of DIE lesions preoperatively. With validation of this model, it has the potential to help surgeons identify which women may have DIE lesions and thus aid in planning the surgical approach to these patients.

In women with endometriosis, the preoperative diagnosis of one type of endometriosis lesion, an endometrioma, is often made by ultrasound. Chapron *et al.*, from the same institution as Lafay Pillet, have previously reported that endometriomas are associated with DIE lesions (Chapron *et al.*, 2009, 2012). Given the recognized association between endometriomas and DIE lesions in their center, additional radiographic studies like an magnetic resonance imaging (MRI) or computed tomography (CT) could be performed as part of the preoperative assessment of ALL women with endometriomas or ovarian cysts to help identify DIE lesions and assist in surgical planning. But, as only about half of the women with endometriomas have DIE lesions and not all women warranting surgery for ovarian cysts have endometriomas or endometriosis, this approach would subject many women to unnecessary evaluations and would be costly.

It is in the setting of endometriomas that the present study is conducted. Lafay Pillet *et al.* develop the first clinical model using the reproductive history and clinical symptoms of women with endometriomas to

predict which women might also have deep infiltrating endometriosis lesions (Lafay Pillet *et al.*, 2014). They reason that restricting the model to endometriomas diagnosed at surgery is a sound approach as endometriomas are the only type of endometriosis lesion that is easily diagnosed preoperatively and is associated with DIE lesions. Importantly, they also restrict their study population to those who have complete surgical excision of endometriosis lesions so as to minimize the risk of not ascertaining all women with DIE lesions. Using prospectively collected clinical information from women with endometriomas, they perform first univariate analysis and then logistic regression using the jackknife procedure to tease apart which factors may predict DIE lesions.

These authors find that after systematically obtaining a comprehensive gynecologic history and analyzing the association between various symptoms and DIE, the answers to a few simple questions—moderate pain with gastrointestinal symptoms or intercourse (greater than five on visual analogue scale (VAS)), pain lasting > 24 months, severe dysmenorrhea (prescription of oral contraceptive pill (OCP) for primary dysmenorrhea or worsening of dysmenorrhea) and infertility—may be used to calculate a score to predict which women with endometriomas also have DIE lesions. In cases suggestive of DIE lesions (score > 35), additional radiologic studies may help the skilled surgical team to identify and localize the deep lesions. They propose that using imaging results and clinical symptoms, additional studies, specifically the rectal endoscopic ultrasonography and urologic-CT scan, may aid in identifying DIE lesions.

Treating all endometriosis lesions is one of the major tenets of surgical treatment of endometriosis with the ultimate goal of improving the symptoms of pain and infertility. Of all types of endometriosis lesions, DIE lesions have been most likely to be associated with pain such that their excision results in the greatest improvement in pain (Fauconnier and Chapron, 2005). Interestingly, in this predictive model, three of the four factors associated with DIE lesions are related to pain—dyschezia/dyspareunia, dysmenorrhea and duration of pain. Of these, the

factor most likely to be associated with bowel or rectovaginal deep lesions is the dyschezia/dyspareunia variable which, in turn, contributes most to the predictive score.

The fourth factor, infertility has also improved with surgery, although the role of DIE lesions in infertility has been less certain. Marcoux *et al.* were the first to show that surgical treatment of endometriosis improved fertility in women with minimal and mild endometriosis (Marcoux *et al.*, 1997). That observation was made more clinically relevant when Adamson and Pasta developed the Endometriosis Fertility Index (EFI) (Adamson and Pasta, 2010). This index uses findings at the end of surgical treatment combined with clinical features to predict fertility over the next few years. The role of deep infiltrating lesions in the EFI is limited as the surgical scoring describes the restoration of normal anatomy, which may have little relationship to deep lesions. The EFI has been validated by others (Tomassetti *et al.*, 2013). Additional attention has recently focused on when to excise endometriomas, as their excision may ultimately lead to diminished ovarian reserve and thus impaired fertility (Shah *et al.*, 2014).

The contribution of infertility to the score is less than each of the three other factors. Interestingly, the authors included either primary or secondary infertility in the infertility factor for predicting DIE lesions. As the number of women with secondary infertility is low and similar (~10%) for both those with and without DIE lesions (Table II of Lafay Pillet *et al.*, 2014), it appears that primary infertility may have the greatest contribution to predicting DIE lesions. In this population, nearly 40% of those with endometriomas and DIE lesions have primary infertility compared with only 20% of those with endometriomas without DIE lesions.

In the development of a clinical score to predict DIE lesions, factors are identified which are only associated with the occurrence of DIE lesions. Causality or pathogenesis cannot be inferred. Thus, it is not surprising that substantial pain factors are associated with finding DIE lesions. The association with infertility is surprising however. It is interesting to speculate about what happens to these clinical factors after complete removal of DIE lesions. Will pain be improved? Will infertility?

As all of these women have endometriomas, we can only speculate about the relationship between infertility, DIE lesions and endometriomas. Do these women with primary infertility have more pain interfering with intimacy and preventing them from becoming pregnant? Is the pelvic anatomy more distorted in those with DIE lesions and endometriomas than with endometriomas alone? Does the co-occurrence of endometriomas and DIE lesions reflect a biologic difference in ovulation or in the endometrium which interfere with fertility? Do the DIE lesions themselves alter fertility? Translational research should shed some light on these relationships.

The lack of association of DIE with some factors is not surprising. For example, characteristics we often attribute to women with endometriosis including menorrhagia, early menstruation, age <25 and fainting or school absences during menstruation are not necessarily factors associated with DIE lesions in women with endometriomas. Additionally, bladder or ureteral lesions are less common types of DIE and, in this cohort, occur much less frequently than bowel DIE. Thus, it is not surprising that urinary tract symptoms are not a factor that contributes to the final predictive model as the frequency is too low.

Other observations, however, are less straightforward to interpret. While it is reassuring that women with prior surgery are not more (or less) likely to have DIE lesions, one could imagine that women under care at a center of excellence might have been referred after a surgeon

did not anticipate, recognize or have the expertise to surgically remove a DIE lesion. The relationship between hormone use and pain is also puzzling. Comparing the VAS score in women on and not on hormonal treatment, the VAS score was much higher in those on hormonal treatment (Supplementary Table S2 of Lafay Pillet *et al.*, 2014). It is unclear whether these women were prescribed hormonal treatment in preparation for surgery, suggesting a higher VAS would be indicative of worse disease or whether hormonal treatment was simply ineffective in treating or managing pain. Both explanations are biologically plausible.

The authors are to be commended for systematically collecting comprehensive clinical information on women with endometriomas and their scholarly approach to transforming that data into a clinical scoring system. The validity of the model should be determined by replicating this study in other centers of excellence that have similarly high numbers of patients with deep lesions and endometriomas. The authors' suggestion to assess this scoring system in a group of women who have symptoms suggesting endometriosis but not endometriomas as a means to determine if this relationship between these clinical factors with DIE persists is a provocative idea.

If this proves to be a reliable way of predicting who has DIE lesions, are we any closer to helping women to receive the surgical treatment they need with their first surgery? In animal models of endometriosis, incomplete excision of lesions has been shown to heighten pain (McAllister *et al.*, 2009). These observations together suggest that it is critically important to identify and completely surgically excise deep infiltrating lesions to have the greatest likelihood of long-term improvements in pain. Perhaps complete excision at the first surgery may confer the best outcome.

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