Nonsurgical approaches to the diagnosis and evaluation of endometriosis

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An inability to make the diagnosis of endometriosis or evaluate lesion response to treatment without surgery is a clear impediment to understanding the disease and to developing new therapies. The need is particularly strong for rASRM Stage 1 or 2 disease, since higher stage (rASRM Stage 3 or 4) endometriosis can often be diagnosed by ultrasound or other imaging techniques. Despite promising findings in association studies, no biomarkers or nonsurgical diagnostic or evaluation methods for Stage 1 or Stage 2 endometriosis has yet been clinically validated. Admittedly, validation is difficult, since surgery is required as a gold standard diagnostic method for comparison. This manuscript is aimed as a succinct review of what is known about nonsurgical approaches to detect and assess endometriosis, with an emphasis on Stage 1 and 2. (Fertil Steril® 2024;121:140–4. ©2023 by American Society for Reproductive Medicine.)
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Endometriosis is a chronic, estrogen-dependent inflammatory disease affecting 5%–10% of women of reproductive age, with sequelae that include chronic pelvic pain, dysmenorrhea, scarring, and pelvic organ dysfunction (1–3). The economic impact of this disease is profound, with a yearly cost of diagnosis and treatment exceeding $22 billion in the U.S. alone (4). The gap between onset symptoms and diagnosis is often >6 years (5), largely because of a lack of nonsurgical diagnostic options. Given that endometriosis is often a progressive disease (6) and because surgical removal of lesions is easier and more complete in early-stage disease, earlier diagnosis is critical. Furthermore, because disease can be asymptomatic and symptoms can be affected without altering the underlying disease, the lack of a nonsurgical diagnostic test greatly hampers the ability of researchers to understand who has the disease and how the disease responds to novel therapeutic approaches.

An example of the need for better diagnostic tests is our understanding of the potential role of early-stage endometriosis as a cause of infertility and the controversy surrounding the question of whether the presence of endometriosis should alter our current approach to fertility management (7, 8). Although outcomes after assisted reproductive technology can be queried in large national databases such as those maintained by the Society for Assisted Reproductive Technology (SART) (9), little can be gained without knowing the incidence of endometriosis in the groups compared. In 2019, endometriosis diagnosis was reported in only 2.5% of women undergoing in vitro fertilization (IVF) in the SART database, although many studies using laparoscopy, suggest that the incidence in infertile women likely approaches 50% (10–12), suggesting that approximately 94% of those with endometriosis in the SART database are labeled as not having the disease. This misclassification would clearly bias away from seeing an effect of endometriosis on fertility outcomes.

For all the above reasons, a consensus workshop on research priorities in endometriosis has pointed out that the development of a nonsurgical diagnostic test is critical to moving the field forward (2, 13). Nonsurgical diagnostic tests using symptoms, imaging, blood biomarkers, and tissue biomarkers have been proposed. In this review, I will survey the knowledge landscape around the development of a diagnostic test using these modalities.

SYMPTOM-BASED QUESTIONNAIRES

For clinicians who seldom see endometriosis and for patients searching for a possible explanation of their symptoms, questionnaires can be excellent tools to increase the saliency of endometriosis in a differential diagnosis. It is also possible that such a survey could also increase the consideration of endometriosis among reproductive endocrinology and infertility (REI) physicians.

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Thirty years ago, Forman et al. (14) examined the usefulness of a simple 7-point questionnaire in patients with 2 years of infertility who were already scheduled for a diagnostic laparoscopy, which was done solely for infertility indications. Forty percent of patients had endometriosis diagnosed at surgery, and the most predictive symptom was severe dysmenorrhea, although the symptom survey was not predictive of minimal disease (American Society of Reproductive Medicine stage 1). In the ensuing 30 years, many questionnaires have been developed with the intent to diagnose or screen on the basis of patient-reported symptoms, and these have been extensively described in a scoping review (15). The reviewed studies further reinforced the association of known symptoms, especially dysmenorrhea, with the presence of lesions at laparoscopy. However, as stated in that review, there are no "…fully validated, symptom-based, patient-reported questionnaires for endometriosis screening in adult women." Importantly, none of these surveys would serve to identify a higher risk of the disease in patients whose only symptom is infertility. Subsequent retrospective or population-based studies have used newer techniques to model the impact of symptoms and historical features (16, 17), but these studies depend on a physician diagnosis of endometriosis or not rather than a standard laparoscopic or other clinical evaluation for all subjects. The lack of universal laparoscopy in these studies, then, results in bias in that diagnosis would be made only in people with symptoms that would prompt surgical evaluation by physicians. Although it is theoretically possible that otherwise unappreciated signs or symptoms might be useful for patients with a clinically subtle presentation, the current role of such questionnaires for the REI physician would seem very limited.

IMAGING

Ultrasound and magnetic resonance imaging (MRI) have demonstrated good sensitivity and high specificity in diagnosing advanced-stage endometriosis but often fail to detect early-stage disease. The final two pieces in this *Views and Reviews* are an in-depth exploration of the literature in this discipline. Despite a 2016 Cochrane review (18) concluding that there is insufficient evidence that ultrasound can replace laparoscopy for endometriosis diagnosis, except in the case of ovarian endometriomas, transvaginal ultrasound, using specific techniques, can also detect deep infiltrating endometriosis, with sensitivity enhanced using a bowel preparation (19–23). For rectosigmoid endometriosis, ultrasound has a sensitivity of 80%–91% and a specificity of 94%–97%. A similarly high level of sensitivity and specificity is seen for ovarian endometriomas. Sensitivity for detection of other deep endometriosis lesions (e.g., bladder, uterosacral ligaments, or vagina) is a bit lower, but specificity remains high. Thus, ultrasound is a useful tool for advanced-stage endometriosis, but its ability to detect earlier-stage endometriosis remains poor. Ultrasound remains useful in many cases for surgical planning and as part of the diagnostic evaluation. Furthermore, the "sliding sign" and other maneuvers during transvaginal ultrasound can be useful to detect the presence of significant adhesive disease even in the absence of deeply infiltrating endometriosis (24). Ultrasound innovations, such as targeted nanoparticles, have been used to diagnose and treat endometriosis in a mouse model (25), but the physics of ultrasound and its modest specificity do not currently allow this approach in larger animals, including humans.

Magnetic resonance imaging appears to have a similar sensitivity and specificity to ultrasound (especially three-dimensional ultrasound) in the detection of deeply infiltrating endometriosis (26). Our group has been studying the use of 18-fluorine labeled positron emission tomography probes simultaneously with MRI or computed tomography in both women and rhesus macaques. The rhesus studies do not show sufficient sensitivity for early-stage disease (27) using 16α-[18F]fluoroestradiol, and the human studies using this probe have not yet been published but build on earlier case reports (28) that did not include MRI. Our preliminary conclusion is that 16α-[18F]fluoroestradiol is insufficiently sensitive, and we are working on the use of a progestin-based probe, 21-[18F]fluoro-furanyl-nor-progesterone, with higher affinity and less background in humans. It is my belief that these or other imaging innovations will allow the detection and assessment of peritoneal endometriosis lesions.

BIOMARKERS

In 2016, three systematic reviews on diagnostic, nonsurgical biomarkers for endometriosis were published by Cochrane reviews, focused on urinary, blood, and endometrial tissue analytes (29–31), as well as a separate review of combined nonsurgical modalities (32). The review of eight studies of six urinary biomarkers (30) concluded that no urinary biomarker had been well enough tested to recommend it as a triage test or to replace laparoscopy. The review authors noted that one study (33) found five peptide peaks using liquid chromatography-tandem mass spectrometry that came close (in this single study) to meeting criteria as a triage test and as a replacement for laparoscopy. The lack of additional articles from that group or using these methods suggests that they were not as robust as initial studies suggested.

The review of 141 studies of 122 blood markers (31) also did not find that any biomarker could be shown to be clinically reliable enough to act as a triage test or as a replacement for laparoscopy. The next piece in this *Views and Reviews* series focuses on blood biomarkers. Briefly, only four of the biomarkers (antiendometrial autoantibodies, interleukin-6 (IL-6), carbohydrate antigen-19.9, and carbohydrate antigen-125) had enough studies to provide a meaningful assessment of test accuracy. Thus, many of the remaining biomarkers could be sufficient for a triage or replacement test when further studies are consistent. As of 2020, 18 studies had found 63 different microRNAs (miRNAs) that were differentially expressed in the blood of women with endometriosis compared with controls. Of these 63, however, differential expression of only 14 miRNA species was shared in one or more studies. Some studies using multiple miRNA species for a diagnostic test show significant promise (34) and others show a concerning lack of specificity (35). However,

considerable commercial enthusiasm has developed for the potential for one or more miRNA species to be used in a blood test, with multiple companies testing the efficacy of such markers and posting websites promising future clinical tests. One of these companies, Dot Labs, is currently conducting a multicenter trial (ClinicalTrials.gov NCT04598698), presumably on the basis of the promising initial studies (34) using six miRNA species, showing a receiver operating characteristic area under the curve of 0.939. The use of salivary miRNA-based (and PIWI-interacting RNA) testing is also being explored, but it is too early to determine whether this could be of possible clinical use (36, 37).

Endometrial tissue biomarkers would seem to be the most likely to be useful for endometriosis diagnosis because the tissue is similar to and likely the source of most endometriosis lesions and because they are likely exposed to endocrine and paracrine factors, such as cytokines, produced by nearby lesions in higher amounts than the rest of the body. The Cochrane review of 54 studies of endometrial biomarkers (29) concluded that only two of the reported endometrial biomarkers (protein gene product [PGP] 9.5 and CYP19) had sufficient data to be evaluated. Of these, PGP 9.5, a nerve fiber marker, appeared to meet criteria to replace laparoscopy for diagnosis after discarding an outlier study with a sensitivity of 0.96 and a specificity of 0.86, although CYP19 did not meet the triage or replacement test criteria with a sensitivity of 0.77 and a specificity of 0.74. The remaining data were insufficient to be subjected to meta-analysis, but biomarkers identified (17EHSD2, IL-1R2, caldesmon) and neural markers (vasoactive intestinal peptide, calcitonin gene-related peptide, substance P, and neuropeptide Y) were deemed of interest for further study. Further work on PGP 9.5 demonstrated a sensitivity of 55.4% and a specificity of 92.7%, and the sensitivity of the test improved to approximately 68% when a deep endometrial biopsy was performed using a uterine curette. These estimated test characteristics are not sufficient for a replacement or triage test, but more study is needed.

The first clinically used endometrial biomarker for endometriosis was absent midsecretory endometrial immunostaining for the $\beta 3$ integrin subunit. The test, formerly marketed in the U.S. as "E-tegrity," was developed on the basis of the fundamental discovery of marked and rapid alterations of integrin subunit expression over the menstrual cycle (38). Expression of the $\beta 3$ integrin subunit was correlated with IVF success (39) and studies in animal models showed the likely functional relevance of $\beta 3$ integrin during embryo implantation (40, 41). In addition, the finding that lack of expression was correlated tightly with a diagnosis of endometriosis (42) encouraged further clinical use. This finding was not replicated in a much smaller study using similar methods (43). Furthermore, the patients in the original study would have been classified as having unexplained infertility had not endometriosis been identified, and it remains unclear whether the immunostaining reflects the infertility or the endometriosis. Notably, $\beta 3$ integrin immunostaining is correlated highly with epithelial histological changes, and a lag in those changes (sometimes referred to as out of phase) will result in negative staining. Because an epithelial lag is common in healthy women (44), the clinical use of $\beta 3$ integrin testing is minimized. The relationships between endometriosis, endometrial receptivity, and $\beta 3$ integrin continue to be studied (45), but clinical application of $\beta 3$ integrin as an individual biomarker remains of very limited use.

A more recent endometrial test is immunostaining for BCL6 protein (please note my conflict of interest in this area). Early evidence suggested a very high sensitivity and specificity for using BCL6 immunostaining as an endometriosis biomarker (46). Independent clinical evidence (47, 48) confirmed increased staining in women with endometriosis. Furthermore, a similar increase in BCL6 was seen after endometriosis induction in a baboon model (49), bolstering the hypothesis of a tight association between the disease and the test positivity. Further interest was garnered by observational studies in women correlating pregnancy rate in IVF and embryo transfer with BCL6 immunostaining (50) and demonstrating an increased IVF success when BCL6 positive patients were treated for endometriosis before embryo transfer (51). Another study, using a different antibody, a different detection method, a different patient population, and a cutoff value with unclear rationale, did not confirm BCL6 as a predictor of embryo implantation (52). However, despite methodological differences, these data clearly indicate the need for more research to validate the characteristics of the commercially available test in different patient populations (53). The identification of a partner protein for BCL6, SIRT1, whose overexpression in women with endometriosis largely mirrors that of BCL6 and which has been shown to interact directly with BCL6 has added a potential for SIRT1 immunostaining to improve the test characteristics of BCL6 immunostaining, especially given the independent verification of SIRT1 overexpression in women with endometriosis (49, 54, 55). The clinical usefulness of BCL6 and SIRT1 immunostaining remains to be validated, but the present an exciting possibility for both endometriosis diagnosis and evaluation of uterine receptivity.

CONCLUSIONS

Despite much work in the area, a nonsurgical diagnostic technique for early-stage endometriosis remains to be developed, or at least fully validated. Questionnaires, in isolation, are unlikely to be helpful for the REI physician. Although imaging-based diagnosis is robust for deep infiltrating disease and ovarian endometriomas, novel imaging techniques such as those in ongoing studies of positron emission tomography probes and MRI techniques will need to be tested. In the next 5 years, developing information about blood miRNA and endometrial tissue BCL6 and/or SIRT1 immunostaining should help to better understand the usefulness of these tests. Other tissue markers, including 17EHSD2, IL-1R2, caldesmon, and neural markers such as vasoactive intestinal peptide, calcitonin gene-related peptide, substance P, and neuropeptide Y, are likely deserving of further study. However, the lack of publications about these biomarkers over the last 8 or more years and the difficulty of publishing "negative data" suggest the possibility that these biomarkers failed further validation. It is also possible that novel combinations

of biomarkers, potentially aided by machine-learning algorithms (56), will improve their diagnostic ability. We must also contemplate the possibility that the failed validation of so many prior candidate biomarkers and diagnostic techniques (31) reflects substantial disease heterogeneity, which prevents the use of a universal set of biomarkers. It is believed that ongoing international efforts to better describe and standardize endometriosis subtypes (57) will allow a better understanding of this heterogeneity and the development of subtype-specific testing.

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Steven L. Young: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

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