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Commentary

Emerging Diagnostic Tools for the Early Diagnosis of Endometriosis

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Endometriosis is a common, burdensome, chronic disease that affects more than 11% of United States (US) women of reproductive age. Worldwide, endometriosis affects approximately 190 million women [1]. Endometriosis occurs when tissues normally found inside the lining of the uterus migrate and grow in other locations, most commonly the ovaries, fallopian tubes, and other organs. These circumstances may cause life-altering consequences [2]. The etiologies of endometriosis remain unclear, although, retrograde menstrual flow is perhaps the most plausible mechanism. Other possible etiologic factors include genetic, immunological, and hormonal as well as previous pelvic surgery, most notably Cesarean delivery (C-section) [3]. Ectopic endometrium cycles on the same schedule as normal menses but is trapped within the implanted tissues. Consequently, endometriotic implants create scar tissue or produce masses in the uterine wall (adenomyoma), ovaries (endometrioma), pelvic peritoneum and other tissues. They elicit proinflammatory cytokines with greater affinities for impacted sites, such as scars from recent surgery. The most common symptoms of endometriosis include abdominal pain and cramping before, during, and after menstruation, dyspareunia, pain with defecation or urination, excessive menstrual bleeding, and infertility [1]. These symptoms are nonspecific and may involve a range of etiologies, and are often treated empirically using medications that reduce or eliminate menstrual bleeding and pain. While the efficiency of empiric treatment is important, this strategy may miss an opportunity to make a specific diagnosis that can inform treatment decisions, particularly in women who desire childbearing.

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In the US and worldwide, the early diagnosis of endometriosis remains a major clinical and public health challenge. The average time to diagnose endometriosis in the US as well as globally has been estimated to be 7 years after the onset of symptoms [1]. At present, in addition to a careful review of the patient's medical history and physical examination, the most commonly employed, as well as most accurate, procedures to diagnose endometriosis include pelvic examinations, abdominal ultrasound, magnetic resonance imaging (MRI), and laparoscopy. In the diagnosis of endometriosis, gynecologists have considered laparoscopic surgery to be the gold standard. This procedure, however, can be costly and confers possible risks of surgical complications [1]. In addition, the accuracy of laparoscopy depends on factors such as the experience of the surgeon as well as the stage of the disease.

The ideal test for early diagnosis of endometriosis would use symptom-based criteria that define test eligibility and then establish the best test result cut-points to optimize sensitivity and specificity. A test with high predictive values would ideally rule-in endometriosis if positive and rule it out if negative. Suboptimal tests can be helpful in reducing the number of individuals who move on to more invasive testing, such as laparoscopy. In this Commentary we performed a PubMed Search to identify promising approaches. We highlight several promising but unproven emerging diagnostic tools in various stages of development and evaluation in the early diagnosis of endometriosis.

Endometriosis is characterized by changes in the environmental balance of progesterone and estrogen which are the primary causes of angiogenesis, apoptosis, immunological responses, and inflammation. These circumstances have led to the development of diagnostic tools that rely on detecting biomarkers that may signal the presence of endometriosis due to these changes. These include hematologic and salivary markers of messenger ribonucleic acid (mRNA) fragments [4]. To date, however, biomarkers have demonstrated low accuracy in detecting endometriosis. In addition, the accuracy of non-invasive methods of diagnosis such as MRI and transvaginal ultrasound seem acceptable only for advanced stages of endometriosis. Recent research has focused on the use of machine-learning algorithms such as random forest and decision tree approaches to diagnose endometriosis. These approaches rely on comorbidities but yield relatively low sensitivities, specificities as well as predictive values in diagnosing endometriosis. In recent years, there have been attempts to rely more on noninvasive methods in the context of medical histories that include gynecologic and family exposures as well as careful pelvic examinations. Due to their limitations, these noninvasive diagnostic methods have not, at present, produced the hypothesized benefits for early diagnosis of endometriosis.

Myoelectric activity in the gastrointestinal tract has recently been considered as a potential diagnostic modality for endometriosis. Myoelectric activity in the gastrointestinal tract can be detected noninvasively with an electrogastrogram (EGG). When applied to the small intestine to detect gastrointestinal myoelectric activity, the technique is called electroviscerography (EVG). EVG monitoring by a similar EGG device has been cleared by the US Food and Drug

Administration (FDA). At present EVG is being deployed as a non-invasive, 30-minute clinical diagnostic tool for gastroparesis [5]. It is plausible, but unproven, that this method may detect the presence of a unique digital fingerprint of myoelectric activity associated with endometriosis in the small intestine. If so, this technology would detect the characteristic abnormal contraction of the small bowel due to the initial production and presence of abnormal endometrial tissue within the peritoneal cavity. This, in turn, would result in the technology representing a non-invasive means to diagnose early-onset endometriosis.

At present, there is no US FDA-cleared non-invasive diagnostic test for endometriosis. For EVG and other emergent technologies, peer-reviewed analytic studies are needed to establish the optimal patient criteria and test result thresholds that will be most useful for clinical decision-making [6]. These studies should include women with abdominal pain with and without infertility as this may yield very different sensitivities, specificities and predictive values. Early diagnosis of endometriosis remains a clinical and public health challenge, with a succession of promising approaches ultimately not bearing fruit, thus far. Once new technologies such as EVG are more fully evaluated, they may give clinicians the post-test certainty they need to transition from symptom-based to diagnosis-based treatment. On the other hand, this may turn out to be what Thomas Henry Huxley, referred to when commenting on the great tragedy of science… "another beautiful hypothesis, slain by ugly facts" [7].

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Conflict of Interest

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