Can we accurately diagnose endometriosis without a diagnostic laparoscopy?

Camran Nezhat1-3, Shruti Agarwal1,2, Deborah Ann Lee1,2, Mahkam Tavallaee1,2

1Center for Special Minimally Invasive and Robotic Surgery, Camran Nezhat Institute, Woodside, California, United States of America
2Stanford University Medical Center, Palo Alto, California, United States of America
3University of California San Francisco, San Francisco, California, United States of America

Abstract

Endometriosis is a progressive, estrogen-dependent, chronic inflammatory disease that affects approximately 6-10% of reproductive age women. Patients usually present with symptoms, such as non-menstrual pelvic and abdominal pain, ovulatory pain, dyspareunia, dysmenorrhea, dyschezia, and/or changes to bowel or bladder function, which can be exacerbated during ovulation or menses. Endometriosis is a leading cause of unexplained infertility, accounting for up to 50-80% of cases. Currently, altered endometrial receptivity and progesterone resistance are some of the leading theories that could explain endometriosis-related implantation failure. In the endometrium, the B-cell chronic lymphocytic leukemia/lymphoma 6 (BCL-6) protein forms a complex that binds to and inactivates regulators of the progesterone pathway, leading to progesterone resistance, aberrant decidualization, implantation failure, and recurrent miscarriages in women diagnosed with endometriosis. Surgical diagnosis consisting of laparoscopy, with or without histologic confirmation, is still considered the gold standard for diagnosis of endometriosis. Development of noninvasive screening and diagnostic tests to accurately identify patients with endometriosis has become increasing popular. A screening test for endometriosis has been developed to detect endometrial BCL-6 overexpression in asymptomatic women with unexplained infertility or recurrent pregnancy loss. Positive endometrial BCL-6 testing has been associated with recurrent miscarriages and poor in vitro fertilization outcomes. When the underlying cause of endometrial inflammation secondary to endometriosis was treated, an improvement in subsequent live birth rates was seen. Endometrial BCL-6 testing has a high positive predictive value that could help physicians and patients undergoing infertility treatment to seek surgical evaluation for endometriosis, to improve their reproductive outcomes. (J Turk Ger Gynecol Assoc 2022; 23: 117-9)

Keywords: Infertility, endometrioma, endometriosis, laparoscopic surgery, ReceptivaDx

Received: 03 February, 2022 Accepted: 20 May, 2022

Introduction

Endometriosis is considered a progressive, estrogen-dependent, chronic inflammatory disease that affects approximately 6-10% of reproductive age women, with over 200 million women worldwide estimated to be affected (1). Endometriosis can be found in multiple areas of the human body, with extragenital endometriosis leading to thoracic, genitourinary, gastrointestinal, and/or nervous system dysfunction. Patients usually present with symptoms such as non-menstrual pelvic and abdominal pain, ovulatory pain, dyspareunia, dysmenorrhea, dyschezia, and/or changes to bowel or bladder function, which can be exacerbated during ovulation or menses. Extragential symptoms can also be seen: shoulder pain associated with diaphragmatic endometriosis; upper abdominal pain with pancreatic endometriosis and lumbar pain with sciatic nerve endometriosis; and chest
pain, hemoptysis and lung collapse in cases of pulmonary endometriosis (2-5). The severity of symptoms can vary from mild to severe, with up to 25% of women being completely asymptomatic (6). In some patients, the only presenting sign of endometriosis may be unexplained infertility, with multiple failed in vitro fertilization (IVF) treatments causing increased suspicion.

Endometriosis is a leading cause of unexplained infertility, accounting for up to 50-80% of women (7). Infertility caused by endometriosis can be explained by several hypotheses including abnormal utero-tubal transport, ovulatory dysfunction, altered cell-mediated immunity, distorted pelvic anatomy, dysynchronous oocyte maturation, altered endometrial receptivity and decreased oocyte quality (8). Currently, altered endometrial receptivity and progesterone resistance are some of the leading hypothetical mechanisms that could explain endometriosis-related implantation failure. These hypotheses are based on the need for adequate progesterone levels and endometrial receptor expression for embryo implantation, endometrial stabilization and maintenance of pregnancy and any mechanism that interferes with progesterone signaling can cause implantation failure (9-12).

Endometriosis has been associated with aberrant humoral and cellular immunity (12). B-cell chronic lymphocytic leukemia/lymphoma 6 (BCL-6) is a protein encoded by a proto-oncogene present on chromosome 3 (3q27.3) that stimulates inflammatory cytokines such as interleukin-6 (IL-6), IL-8, and IL-17 in the peritoneal fluid of women with endometriosis. In the endometrium, BCL-6 forms a complex that binds to and inactivates regulators of the progesterone pathway, leading to progesterone resistance, aberrant decidualization, implantation failure, and recurrent miscarriages in women diagnosed with endometriosis (8,10-14).

Surgical diagnosis consisting of laparoscopy, with or without histologic confirmation, is still considered the gold standard for the diagnosis of endometriosis. When endometriomas are involved, this can become difficult, as endometrioma subtypes are treated differently in patients desiring to preserve fertility. Type 1 endometriomas arise from implanted endometrial-like tissue on the ovarian cortex (Figure 1A-C). To minimize adverse effects on ovarian reserve and fertility, these are treated by brushing or washing off the lesions. Type 2 endometriomas arise from functional cysts that are invaded by endometrial-like implants. When less than 50% invasion is involved, excision can be performed successfully without compromising ovarian reserve (15-18).

Development of non-invasive screening and diagnostic tests to accurately identify patients with endometriosis has become increasingly popular (14). A screening test for endometriosis called ReceptivaDx (CiceroDx, Huntington Beach, CA, USA) has been developed to detect endometrial BCL-6 overexpression in asymptomatic women with unexplained infertility or recurrent pregnancy loss (19). This test also detects beta-3 integrin expression, a cell adhesion molecule integral to successful implantation (11,13). Positive endometrial BCL-6 testing, defined as an HSCORE >1.4, has been associated with recurrent miscarriages and poor IVF outcomes (13,20,21). When the underlying cause of endometrial inflammation secondary to endometriosis was treated, an improvement in

Figure 1. (A-C) Type 1 endometriomas from implanted endometrial-like tissue on the ovarian cortex.
subsequent live birth rates was seen (50-76%) when compared to controls (7.4%). In this study, 93.8% of patients that tested positive for BCL-6 had laparoscopic findings of endometriosis (19). A retrospective study by Nezhat et al. (22) on reproductive age females going through IVF treatment with endometrial BCL-6 overexpression who underwent laparoscopic surgery for treatment of suspected endometriosis showed that three-quarters of patients (74.7%, n=56) had a histologically confirmed diagnosis, while 21.3% were diagnosed visually through the presence of ovarian endometriotic implants (n=16). Women with at least six months of postoperative follow-up were assessed for reproductive outcomes (n=40), resulting in a clinical pregnancy rate of 90.0%. The positive predictive value (PPV) of BCL-6 testing was found to be as high as 96% for the diagnosis of endometriosis, similar to previously reported rates (19,22).

**Conclusion**

According to ASRM, approximately 50% of patients with unexplained infertility may have undiagnosed endometriosis (8). Although women diagnosed with unexplained infertility and recurrent pregnancy loss undergo IVF treatments, they seldom seek surgical diagnosis of endometriosis, even though persistent endometriosis could affect the success rate of IVF. Testing for endometrial BCL-6 may help determine high-risk endometriosis patients with other inflammatory pathologies who could be good surgical candidates. Endometrial BCL-6 testing has a high PPV that could help physicians and patients undergoing infertility treatment to seek surgical evaluation for endometriosis, to improve their reproductive outcomes (22).

**Peer-review:** Externally and internally peer-reviewed.

**Conflict of Interest:** No conflict of interest is declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

**References**

1. Nezhat C, Li A, Abed S, Ballassiano E, Saliemannjad R, Nezhat A, et al. Strong Association Between Endometriosis and Symptomatic Leiomyomas. JLS 2016; 20: e2016.00053.
2. Veeraswamy A, Lewis M, Mann A, Kotikela S, Hajhosseini B, Nezhat C. Extragenital endometriosis. Clin Obstet Gynecol 2010; 53: 449-66.
3. Nezhat C, Falik R, McKinney S, King LP. Pathophysiology and management of urinary tract endometriosis. Nat Rev Urol 2017; 14: 359-72.
4. Nezhat C, Li A, Falik R, Copeland D, Razavi G, Shakib A, et al. Bowel endometriosis: diagnosis and management. Am J Obstet Gynecol 2018; 218: 549-62.
5. Nezhat C, Lindheim SR, Backhus L, Vu M, Vang N, Nezhat A, et al. Thoracic Endometriosis Syndrome: A Review of Diagnosis and Management. JSLS 2019; 23: e2019.00029.
6. Bulleotti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. J Assist Reprod Genet 2010; 27: 441-7.
7. Litman E, Giudice L, Lathi R, Berker B, Milki A, Nezhat C. Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. Fertil Steril 2005; 84: 1574-8.
8. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. Fertil Steril 2012; 98: 591-8.
9. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am 2012; 39: 535-49.
10. Burney RO, Talbi S, Hamilton AE, Vo KC, Nyegaard M, Nezhat CR, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology 2007; 148: 3814-26.
11. Lessey BA, Kim JJ. Endometrial receptivity in the eutopic endometrium of women with endometriosis: it is affected, and let me show you why Fertil Steril 2017; 108: 19-27.
12. Miller JE, Ahn SH, Monsanto SP, Khalaj K, Koti M, Tayade C. Implications of immune dysfunction on endometriosis associated infertility. Oncotarget 2017; 8: 7138-47.
13. Lessey BA, Young SL. What exactly is endometrial receptivity? Fertil Steril 2019; 111: 611-7.
14. Agarwal SK, Chapron C, Giudice LC, Lauffer MR, Leyland N, Missmer SA, et al. Clinical diagnosis of endometriosis: a call to action. Am J Obstet Gynecol 2019; 220: 354e1-12.
15. Nezhat F, Nezhat C, Allan CJ, Metzger DA, Sears DL. Clinical and histologic classification of endometriomas. Implications for a mechanism of pathogenesis. J Reprod Med 1992; 37: 771-6.
16. Nezhat C, Nezhat F, Nezhat C, Seidman DS. Classification of endometriosis. Improving the classification of endometriotic ovarian cysts. HUM Reprod 1994; 9: 2212-3.
17. Falik RC, Li A, Farrimound F, Razavi GM, Nezhat C, Nezhat F. Endometriomas: classification and surgical management. OBG Manag 2017; 29: 38-43.
18. Donnez J, Lousse JC, Jadoul P, Donnez O, Endometriotic cyst management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. Fertil Steril 2010; 94: 28-32.
19. Evans-Hoeker E, Lessey BA, Jeong JW, Savaris RF, Palominow WA, Yuan L, et al. Endometrial BCL6 Overexpression in Eutopic Endometrium of Women With Endometriosis. Reprod Sci 2016; 23: 1234-41.
20. Almquist LD, Likes CE, Stone B, Brown KR, Savaris R, Forstein DA, et al. Endometrial BCL6 testing for the prediction of in vitro fertilization outcomes: a cohort study. Fertil Steril 2017; 108: 1063-9.
21. Likes CE, Cooper LJ, Efird J, Forstein DA, Miller PB, Savaris R, et al. Medical or surgical treatment before embryo transfer improves outcomes in women with abnormal endometrial BCL6 expression. J Assist Reprod Genet 2019; 36: 483-90.
22. Nezhat C, Rambhatla A, Miranda-Silva C, Asiai A, Nguyen K, Eyvazadeh A, et al. BCL-6 Overexpression as a Predictor for Endometriosis in Patients Undergoing In Vitro Fertilization. JSLS 2020; 24: e2020.00064.