



Can we accurately diagnose endometriosis without a diagnostic laparoscopy?

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Abstract

Endometriosis is a progressive, estrogen-dependent, chronic inflammatory disease that affects approximately 6-10% of reproductive age women. Patients usually presents 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)

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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. Extragenital 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



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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 patient, 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, dyssynchronous 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

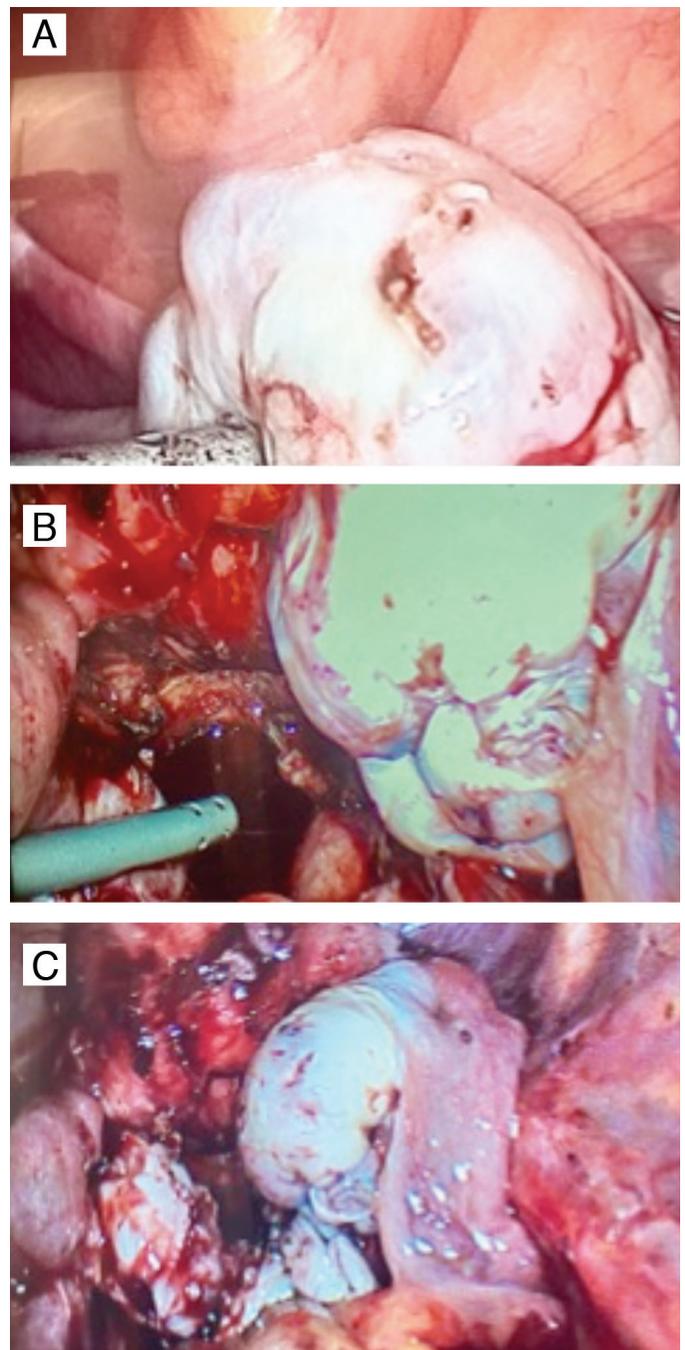


Figure 1. (A-C) Type 1 endometriomas from implanted endometrial-like tissue on the ovarian cortex

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).

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