Fibrosis as a molecular hallmark of endometriosis pathophysiology

The pathogenesis and pathophysiology of endometriosis remain areas of active investigation because thorough understanding of disease process is prerequisite to progress in the areas of biomarker discovery and nonhormonal treatment approaches. The established molecular hallmarks of endometriosis include estrogen dependence, chronic inflammation, neoneuroangiogenesis, and attenuated progesterone responsiveness. Compelling evidence also exists to support fibrosis as a molecular hallmark of endometriosis pathophysiology.

Fibrosis is characterized by the development of fibrous connective tissue resulting from repetitive tissue injury and repair. At the cellular level, myofibroblasts are central to the process of fibrosis. Once activated, myofibroblasts proliferate and produce collagenous extracellular matrix, which both heals and disrupts the surrounding cytoarchitecture. Often described surgically as "scarring," fibrotic tissue is mechanically stiff, opaque-appearing, relatively avascular, and often distortional, thereby complicating surgical dissection. Activated myofibroblasts in endometriotic lesions are detected based on the presence of α-smooth muscle actin (α-SMA). The evidence for the presence of activated myofibroblasts, detected using α-SMA immunohistochemistry, as a consistent feature of peritoneal, ovarian, and deep infiltrating endometriotic lesions has been well reviewed (1).

Interestingly, fibrosis as a histologic feature in lesions may be progressive, likely because of repetitive tissue injury and repair. Indeed, in a nonhuman primate model of endometriosis, the prevalent phenotype of peritoneal lesions changed from red vesicular to white fibrotic over time and was corroborated at the molecular level by a significantly increased expression of α-SMA in endometriotic lesions with time since induction (2). During this fibrotic progression, lesions can lose typical features of endometrial glands and stroma evidenced at implantation, thereby confounding the histologic confirmation of disease. This may explain the discordance reported between the surgical impression of peritoneal endometriosis and its histopathologic definition, a difference more often observed in biopsies of white fibrotic lesions than in those of the red vesicular phenotype. However, if orthogonally confirmed, the reliable accumulation of markers of fibrosis, such as α-SMA, as a function of time presents the intriguing prospect of immunohistochemically dating endometriosis lesions.

Ovarian endometriomas present unique management challenges in patients of reproductive age with pelvic pain. Commonly referred to as "chocolate cysts" due to the accumulation of dark-brown fluid, ovarian endometriomas are associated with infertility, reduced serum antimüllerian hormone (AMH) levels, and dysmenorrhea. The surgical management of endometrioma in patients with both pain and infertility is currently individualized, with careful consideration of risks, including the risk of inadvertent damage to the ovarian reserve.

Although the threshold for endometrioma size to triage surgical decision making requires further study, laparoscopic cystectomy for endometriomas >4 cm may improve the odds of achieving pregnancy and has been associated with improved pain scores after surgery. Unfortunately, endometrioma recurrence after cystectomy is observed in as many as one third of treated patients (3).

In this issue of *Fertility and Sterility*, Nie et al. (4) explore a role for fibrosis underpinning the association between ovarian endometrioma and both dysmenorrhea and reduced AMH levels. In a cohort of 313 women who underwent laparoscopic cystectomy (specifically using the cyst stripping technique) for ovarian endometrioma, markers of fibrosis as well as established markers for recurrence were evaluated in endometrioma specimens using immunohistochemistry. The investigators reported that the extent of fibrosis in the endometrioma lesion positively correlated with the severity of dysmenorrhea, as measured by visual analog scale scores. It should be noted that the co-occurrence of endometrioma with peritoneal endometriosis at the time of surgery also correlated with dysmenorrhea scores, consistent with the findings of a large observational study (5), thereby rendering relative contributions of ovarian and peritoneal lesions to dysmenorrhea unclear.

The levels of AMH were negatively correlated with the extent of cortical fibrosis adjacent to the endometrioma, as evaluated using Masson trichrome staining. This perspective was made possible by the removal of some ovarian cortical tissue adjacent to the endometrioma cyst wall at the time of cystectomy in a subset of patients. Interestingly, cortical fibrosis has been associated with ovarian reserve decline in women exposed to chemotherapy, suggesting this process may be a common mechanistic pathway for follicular depletion.

The correlation between increased cortical fibrosis and reduced AMH levels in women with ovarian endometrioma advances our understanding of the pathophysiology of endometriosis, particularly if reduced AMH levels are an accurate reflection of follicle depletion in these patients (preoperative antral follicle count was not reported). These observations require validation, and the timeline from endometrioma formation to adjacent cortical fibrosis and the follicle pool impacts are unknown and possibly variable. Yet, this finding, in concert with those of others, highlights ovarian reserve depletion as an area of overlap in the Venn diagram of ovarian endometrioma and infertility.

Importantly, preclinical and molecular lines of evidence support fibrosis to be an iteratively progressive, time-dependent process, with preventive and interventional implications. Recent studies elucidating the mechanisms involved in fibrogenesis have revealed new candidates for mitigation, such as transforming growth factor-β1, hyaluronan synthase 2 (HAS2), and platelet-derived growth factor receptor, and several antifibrotic agents have demonstrated promise in animal studies. Additionally, the evidence linking endometrioma and reduced AMH levels has introduced an additional variable in the shared approach to ovarian

endometrioma(s) in patients with infertility and a potentially important consideration in the counseling and management of women with endometrioma who desire future fertility. To inform clinical decision making in these contexts, well-designed, longitudinal studies are needed.

Although gynecologic surgeons have for years recognized the complicating impact of fibrosis in the surgical management of endometriosis, the molecular mechanisms underpinning the relationship of fibrosis with endometriosis-associated pain and infertility are clarifying. The study by Nie et al. (4) advances our understanding of the clinical translational impacts of fibrosis, particularly the relationship between ovarian endometrioma and ovarian reserve, and contributes to the appreciation of fibrosis as a molecular hallmark of endometriosis pathophysiology.

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