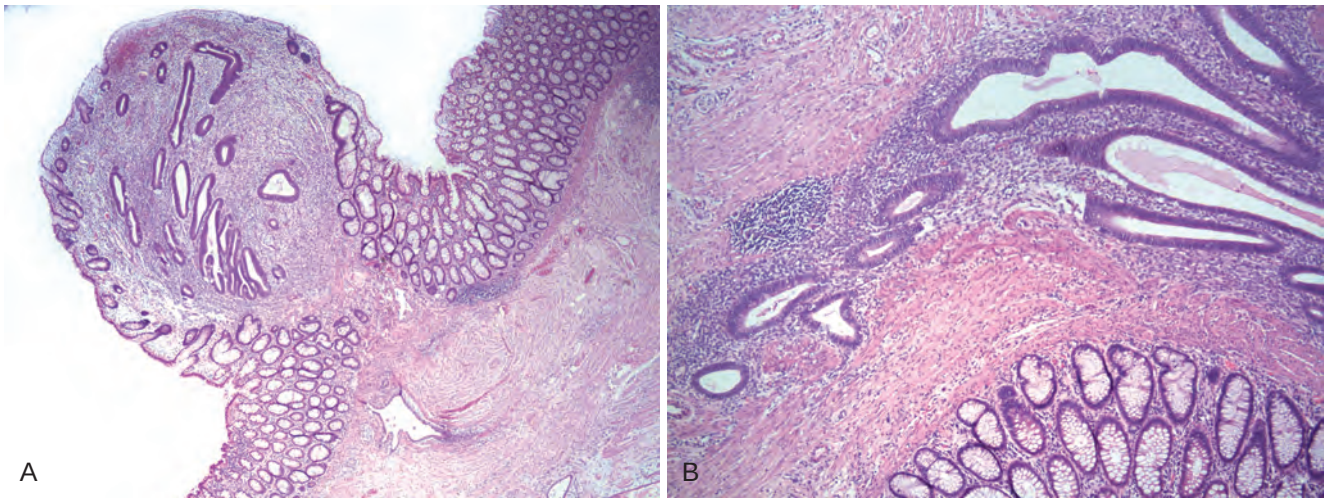

Figure 22-21 Endometriosis. **A,** Endometriosis involving the mucosa of the colon. **B,** Higher magnification reveals endometrial glands and stroma adjacent to normal colonic mucosa.

The regurgitation theory provides a plausible explanation for the anatomic location of ectopic endometrial tissue in the vast majority of cases. However, it cannot explain all cases, such as endometriosis in women who are amenorrheic because of a variety of underlying etiologies (e.g., gonadal dysgenesis); endometriosis in the urogenital tract of men treated with high-dose estrogens for prostate cancer; and endometriosis in distant sites like the brain, lung and bone. In addition, the relatively low incidence of endometriosis, despite the common occurrence of retrograde menstruation (up to 90% of women), suggests that additional factors must be involved in the pathogenesis of the disorder.

Molecular analyses have provided additional insights into the pathogenesis of endometriosis. The endometriotic implants show certain differences when compared to the endometria of women without endometriosis (Fig. 22-22). These include the following:

- *Release of proinflammatory and other factors*, including PGE2, IL-1β, TNFα, IL-6 and -8, NGF, VEGF, MCP-1, MMPs, and TIMPs.
- *Increased estrogen production by endometriotic stromal cells*, due in large part to high levels of the key steroidogenic enzyme aromatase, which is absent in normal endometrial stroma. Estrogen enhances the survival and persistence of endometriotic tissue, and inhibitors of aromatase are beneficial in the treatment of endometriosis. A link between inflammation and estrogen production is made plausible by the ability of prostaglandin E_2 to stimulate local synthesis of estrogen.

  The expression of these factors contributes to the survival of ectopic endometrial tissue by promoting invasion and the establishment of neurovascular networks and by decreasing immune clearance. In addition, epigenetic alterations have been described that lead to increase responsiveness to estrogen and decreased responsiveness to progesterone, alterations that promote endometrial proliferation and survival. These abnormalities are present not only in ectopic endometriotic tissue, but also, albeit to a lesser degree, in the uterine endometrium of patients with endometriosis, suggesting that there is a fundamental defect in the endometrium.
- An association between endometriosis and ovarian cancer of the endometrioid and clear cell types (discussed later) has been noted in a number of epidemiologic studies with an approximate threefold increase in women with endometriosis. More recent molecular studies have demonstrated shared mutations in specific genes (*PTEN* and *ARID1A*) in endometriotic cysts, atypical endometriosis (see later) and associated carcinomas. These studies suggest a common origin of abnormal

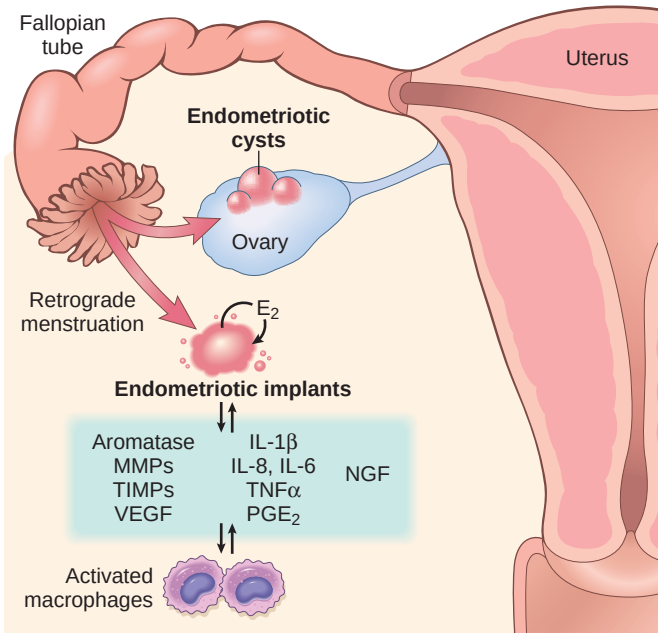

Figure 22-22 Pathogenesis of endometriosis. The factors expressed in endometriotic implants, eutopic endometrium and activated macrophages that play a role in the establishment and maintenance of endometriotic implants.