Endometriosis and adenomyosis: shared pathophysiology

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Endometriosis and adenomyosis are closely related disorders. Their pathophysiologies are extremely similar. Both tissues originate from the eutopically located intracavitary endometrium. Oligoclones of endometrial glandular epithelial cells with somatic mutations and attached stromal cells may give rise to endometriosis if they travel to peritoneal surfaces or the ovary via retrograde menstruation and/or may be entrapped in the myometrium to give rise to adenomyosis. In both instances, the endometrial cell populations possess survival and growth capabilities conferred by somatic epithelial mutations and epigenetic abnormalities in stromal cells. Activating mutations of KRAS are the most commonly found genetic variant in endometriotic epithelial cells, whereas the adenomyotic epithelial cells almost exclusively bear KRAS mutations. Epigenetic abnormalities in the stromal cells of endometriosis and adenomyosis are very similar and involve an abnormal expression pattern of nuclear receptors, including the steroid receptors. These epigenetic defects give rise to excessive local estrogen biosynthesis by aromatase and abnormal estrogen action via estrogen receptor-β. Deficient progesterone receptor expression results in progesterone resistance in both endometriosis and adenomyosis. (Fertil Steril® 2023;119:746–50. ©2023 by American Society for Reproductive Medicine.)

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Pelvic endometriosis is a clinical syndrome characterized by severe dysmenorrhea, chronic pelvic pain, infertility, associated with visualization or histologic demonstration of ectopically located endometrial tissue on the pelvic peritoneum, ovaries, or other pelvic sites such as the bowel (1). A patient with endometriosis experiences these symptoms for a very long time which starts with the adolescent years and extends all the way to menopause (1). When endometrial stromal and epithelial cells line up a hemorrhagic ovarian cyst and respond to estrogen with growth and breakthrough bleeding, this is termed as an ovarian endometrioma or a chocolate cyst. Deep-infiltrating endometriosis usually involves ectopic endometrial tissue embedded in severely inflamed and fibrotic peritoneal tissue, adhered to the vagina and rectum, i.e., the rectovaginal nodule (1).

Retrograde travel of the menstrual blood containing fragments of intrauterine endometrial tissue during ovulatory menses is indispensable for the establishment and progression of pelvic endometriosis (2). This is because identical somatic changes in DNA identified as mutations, discovered in intracavitary endometrial epithelial cells were mapped to the epithelial cells of all 3 forms of pelvic endometriosis, i.e., pelvic peritoneal endometriosis, ovarian endometrioma, and rectovaginal module (2). Moreover, endometrial epithelial cells carrying these specific mutations were enriched in pelvic endometriotic lesions of the same patient, suggesting that special activating-type mutations provide a survival advantage for endometriotic tissues (2).

Adenomyosis is a uterine pathology that is closely related to endometriosis (Table 1) (3). As in the case of endometriosis, adenomyosis is an estrogen-dependent disorder, in which endometrial epithelial cells and stromal fibroblasts are ectopically present in the myometrium as extensions of the normally located endometrium or as islands surrounded by hypertrophic smooth muscle cells (4–6). The symptoms of adenomyosis are quite similar to endometriosis and include heavy menstrual bleeding, dysmenorrhea, chronic pelvic pain, and infertility (Table 1) (6, 7). Although the mechanism of adenomyosis has been debated in the

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past, recent DNA evidence strongly indicates that adenomyosis originates from the invagination of the basal layer of the endometrium into the myometrium (3, 4). In fact, identical somatic mutations were mapped in the normally located basal endometrium to adjacent adenomyotic lesions (3). Although a number of epithelial mutations are found in endometriotic lesions, adenomyotic lesions exclusively exhibit activating mutations of the KRAS gene (3). In contrast to endometriosis, patients with adenomyosis uniquely report a history of pregnancy that is thought to disrupt the endomyometrial junction (Table 1). Repetitious episodes of ovulatory menses, however, are essential in the pathophysiology of both endometriosis and adenomyosis (Fig. 1). Menstruation possibly enhances the entrapment of the basal endometrium in myometrial tissue, hence the process of invagination (3).

Estrogen is essential for the establishment and growth of the ectopic endometrium outside the uterine cavity (3, 4). Therefore, medical strategies blocking both ovarian steroidogenesis and local estrogen synthesis represent an indispensable long-term option for treatment (8). The gonadotropin-releasing hormone analogs, oral contraceptives, or progestins are used to suppress pituitary and ovarian steroidogenesis in both endometriosis and adenomyosis (1, 9, 10). This approach is complemented by judiciously used conservative resection surgery for endometriosis (1). The majority of patients with adenomyosis, however, require a hysterectomy, which is a radical treatment and devastating option for women who desire pregnancy (11, 12).

EPITHELIAL MUTATIONS IN ENDOMETRIOSIS

Two ground-breaking sets of scientific developments over the past 10 years verified that pelvic endometriosis occurs as a result of repetitious episodes of retrograde menstruation, wherein oligoclonal endometrial cells backwashed with blood implant on peritoneal or ovarian surfaces (1, 13). In fact, all 3 forms of endometriosis, i.e., superficial peritoneal, deep-infiltrating, and ovarian endometrioma are explained by this mechanism (1). These new sets of scientific evidence were based on next-generation sequencing of whole exome or whole genome sequencing of endometrial and endometriotic epithelial cells (1, 13). Additional breakthroughs also came from the genomewide characterization of epigenetic defects in endometriotic stromal cells (1). All these studies verified the original concepts that backwashed abnormal eutopic endometrial cells during menstruation are largely responsible for pelvic endometriosis and that estradiol-dependence and progesterone resistance are the key molecular mechanisms responsible for the inflammatory process observed in endometriosis.

Whole exome sequencing revealed that there are >4000 somatic mutations in epithelial cells of matched ovarian endometriomas and eutopic endometrial epithelium samples. Many cancer driver mutations affecting KRAS, PIK3CA, FBXW7, PPP2R1A, and PIK3R1 were detected in most of the examined eutopic endometrial epithelial cells (14). Additionally, similar mutations were found in the majority of endometriotic epithelial samples (14). In matched samples obtained from the same patient, there was a discordance between the distribution of mutations in that PIK3CA was more commonly mutated in the endometrial epithelium whereas KRAS mutations were more commonly encountered in endometriotic epithelial cells (14). However, identical mutations were identified in matched samples of the eutopic endometrium and deep-infiltrating endometriosis in the same patient (15). These findings were consistent with the reports from at least 3 laboratories (Table 2) (14–16). Moreover, identical mutations were mapped to superficial peritoneal and deep-infiltrating endometriosis and ovarian endometriomas in the same patient (17). This recent finding is indicative of eutopic endometrial origin and clonality across all endometriosis lesions, regardless of the subtype (17).

Epithelial PIK3CA mutations were most commonly found in eutopic endometrium, whereas KRAS was the most frequently mutated gene in endometriosis (Table 2). KRAS mutations in endometriosis were limited to amino acids 12, 13, or 61, and resulted in defective guanosine triphosphate hydrolysis, leading to autonomous activation of KRAS (14, 15, 17). This eventually causes constitutive activation of survival pathway cells downstream of KRAS (18). In fact, this may explain the survival advantages conferred on the endometrial oligoclonal cells implanted on pelvic tissues and ovarian inclusion cysts.

EPITHELIAL MUTATIONS IN ADENOMYOSIS

A recent next-generation sequencing study revolutionized our understanding of adenomyosis pathophysiology (16). These investigators went through the pain-staking task of multi-regional sampling of adenomyotic tissue with or without co-existing endometriosis, leiomyoma, and eutopic endometrium (3, 16). Almost all mutations detected in adenomyosis and co-occurring leiomyoma samples were mutually exclusive, indicating the lack of a clonal relationship between adenomyosis and uterine fibroids (16). Therefore, despite their frequent co-occurrence, adenomyosis and leiomyoma seem to be of different pathological origins.

Some mutations detected in adenomyotic lesions, such as those of KRAS and PIK3CA, were also found in the adjacent eutopic endometrium, thus suggesting that these mutations most likely arose in the eutopic endometrial epithelial cells before they invaded the myometrium (16). Intriguingly, identical KRAS mutations were detected in co-existing adenomyotic and endometriotic lesions in several patients (16). Both co-occurring deep-infiltrating endometriotic and ovarian endometrioma tissues revealed KRAS mutations along with adenomyotic tissue in the same patient (16). Together, these findings are suggestive that KRAS-mutated clones arising in the eutopic endometrium attain heightened invasive and survival capacities that facilitate their invasion and growth within the myometrial tissue, thereby establishing adenomyosis.

These gain-of-function type KRAS mutations in adenomyosis were encountered in endometriosis, as well as in cancers of the ovary, lung, pancreatic, and colorectal tissues (19). KRAS mutations in adenomyosis and endometriosis are only found in the epithelial cells and tend to stimulate the

TABLE 1

Clinical Aspects of Endometriosis and Adenomyosis

	Endometriosis	Adenomyosis
Mechanism	Retrograde menstruation and implantation of abnormal oligoclones of endometrial cells on peritoneum or ovary	Disruption of endomyometrial junction followed by invagination and entrapment of abnormal oligoclones of basal endometrial cells within myometrial tissue
Pathology	Endometrial stromal / epithelial cells and histologic evidence of bleeding	Endometrial stromal / epithelial cells and hypertrophic smooth muscle cells
Steroid-response	Responsive to estrogen / progesterone	Less responsive to estrogen / progesterone
Presentation	History of repetitious ovulatory menses Symptoms peak in 20s and 30s	History of term pregnancy or pregnancy loss followed by repetitious ovulatory menses Symptoms peak in 40s and 50s
Symptoms	Dysmenorrhea, chronic pelvic pain, heavy menstrual bleeding, and infertility	Heavy menstrual bleeding, anemia, dysmenorrhea, and infertility

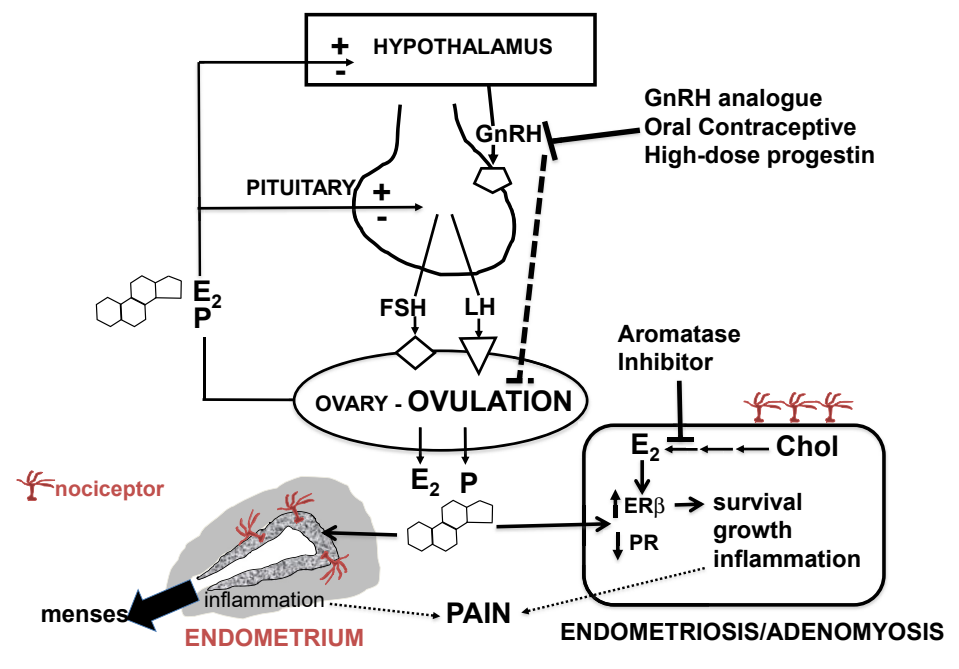
Bulun. Endometriosis, Adenomyosis, and Mechanism. Fertil Steril 2023.

pathways that favor invasion and cell survival (15). Furthermore, KRAS mutations were also linked to progesterone resistance in adenomyosis (16).

EPIGENETIC ABNORMALITIES IN ENDOMETRIOSIS AND ADENOMYOSIS

As emphasized earlier, endometrial or endometriotic stromal cells do not harbor any somatic mutation, perhaps because mesenchymal cell lineages are embryologically programmed in such a way that they do not easily accumulate mutations or go through a malignant transformation, unlike the epithelial cells (1). Endometriotic or adenomyotic stromal cells, however, display a large number of epigenetic abnormalities (1). These abnormalities involve DNA methylation, histone modification, and miRNA expression, which are distinct from the endometrial stromal cells of disease-free patients (1). These altered epigenetic programming mechanisms give rise to abnormal mRNA and protein expression of genes such as aromatase and estrogen and progesterone receptors

FIGURE 1



Recurrent episodes of ovulatory menses are indispensable for both endometriosis and adenomyosis. In the case of endometriosis, oligoclonal endometrial cells in a retrograde menstrual material, implant on the peritoneal surfaces and the ovaries. For adenomyosis, menstruation triggers the entrapment of oligoclonal endometrial cells that invade the myometrium. This is why the interruption of the ovulatory/menstrual process is therapeutic for both conditions. Moreover, ovulation produces large amounts of estradiol, which induces the inflammatory process in both endometriosis and adenomyosis.

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TABLE 2

Estimated Rates of Key Recurrent Mutations in Gynecologic Disorders

Mutations	EE	Adenomyosis	Endometriosis	Leiomyoma
KRAS	++	++++++	+++++	
PIK3CA	++++	+	++++	
PPP2R1A	+	+	+	
ARID1A			+	
MED12				++++++

EE = eutopic (normally located) endometrium.
Modified from Bulun et al. (3).

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in addition to several other nuclear receptors and transcription factors in endometriotic and adenomyotic stromal cells (1).

Estrogen Production and Action

Aromatase enzyme activity and protein expression were discovered in adenomyotic tissue before aromatase expression was demonstrated in endometriosis (20–22). A key nuclear receptor that regulates aromatase (CYP19A1) expression in endometriotic stromal cells is NR5A1 /SF-1) (23, 24). Neither NR5A1 nor its homolog NR5A2 (i.e. LRH-1) has been demonstrated in adenomyosis thus far. Therefore, the mechanism for aromatase expression in adenomyosis is not well understood yet.

The epigenetic mechanisms for aberrant NR5A1 expression in endometriotic stromal cells were studied in detail (25–27). In essence, alternative methylation of CpG sequences in the promoter and coding region of the NR5A1 gene seems to be the key mechanism for its suppression in normal endometrial stromal cells and its expression in endometriotic stromal cells (25–27). The transcription factor, upstream stimulatory factor-2, binds to the demethylated promoter region of the NR5A1 gene to induce its expression in endometriotic stromal cells (28). The binding of NR5A1 to the proximal promoter of the CYP19A1 gene, in turn, is the critical event for aromatase expression in endometriotic stromal cells (23, 29, 30).

Estrogen receptor-a (ESR1) is suppressed, whereas estrogen receptor-b (ESR2) is overexpressed in endometriotic stromal cells (31–33). Similar to NR5A1, ESR2 expression is also regulated by a promoter region that is unmethylated and active in endometriosis, whereas it is methylated and suppressed in the normal endometrium (31, 34). In turn, the ESR2 protein in endometriosis binds to the ESR1 gene promoter and suppresses it (35). A similar pattern of low ESR1 and high ESR2 expression was also observed in adenomyotic tissues (36, 37).

Progesterone resistance. The HSD17B2 gene encodes an enzyme that catalyzes the conversion of estradiol to estrone, inactivating estradiol in the endometrium, placenta, and liver (38). The first scientific clues for progesterone resistance in endometriosis came from the observations that HDS17B2 enzyme activity or expression is severely lower in endometriotic tissue or epithelial cells compared with the normal endometrium (38, 39). In fact, progesterone treatment could not induce the HSD17B2 enzyme activity in endometriotic tissue (39). It was later shown, that in response to progesterone, stromal progesterone receptors were responsible for generating retinoids, which induced HSD17B2 expression in epithelial cells (40–45).

Subsequently, it was discovered that endometriotic stromal cells were severely deficient in progesterone receptors (PGR) (42, 46, 47). In turn, PGR deficiency gives rise to deficient retinol uptake and retinoic acid production by the stromal cells (41, 48). As in endometriosis, PGR expression is also deficient in adenomyotic tissue (16, 49). A recent study also suggested that activating mutations in KRAS are associated with functional progesterone resistance and resistance to progestin treatment in adenomyosis (16).

SUMMARY

Endometriosis and adenomyosis are sister entities with similar molecular mechanisms. Repetitious episodes of ovulation and menstruation are indispensable for both conditions. Clinically, the history of an event that disrupts the endomyometrial junction such as pregnancy, increases the risk of adenomyosis. Abnormal endometrial cells either get entrapped in the myometrium and survive and thrive in this ectopic location or implant, survive, and invade peritoneal surfaces or an involuting corpus luteum cyst (endometrioma) via retrograde menstruation. Activating somatic mutations in KRAS are encountered as the key events in both endometriosis and adenomyosis. In endometriotic epithelial cells, several other genes are also affected by mutations. In adenomyosis, however, epithelial KRAS mutations are almost exclusively found in the great majority of the lesions. The stromal cells of both tissues exhibit widespread epigenetic defects that lead to excessive estrogen formation, abnormal estrogen action via ESR2, and progesterone resistance.

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