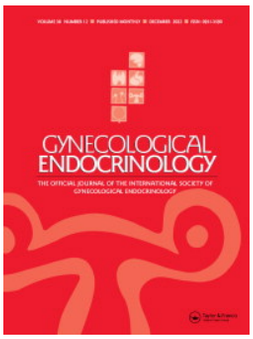

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EDITORIAL
ADENOMYOSIS

Adenomyosis: is an endocrine-related uterine dysfunction?

Adenomyosis is a uterine disorder characterized by dysmenorrhea, abnormal uterine bleeding (AUB), and infertility [1]. Thus, it is a typical condition of menstruating women in their reproductive age, supporting a role of sex steroid hormones implicated in the menstrual cycle. Adenomyosis was considered affecting almost exclusively multiparous women between their 40 s and 50 s, with the diagnosis being confirmed upon hysterectomy performed for AUB [2]. The development of new imaging techniques (i.e. magnetic resonance, transvaginal ultrasound) has changed the diagnosis of adenomyosis, allowing the noninvasive identification of this condition in young women [3]. The association with other uterine disorders, such as endometriosis and fibroids, further highlights a hormonal background. Additionally, adenomyosis is increasingly diagnosed among women with infertility, recurrent pregnancy loss and adverse pregnancy outcomes [1], supporting a link with an endocrine-related uterine dysfunction.

Adenomyosis results from the disruption of the endometrial-myometrial junction, the junctional zone (JZ), with the invasion of the myometrium by endometrial glands and stroma, resulting in ectopic endometrial islands that induce hypertrophy in the adjacent myometrial smooth muscle cells [4]. The trigger of the initial phenomenon is still unknown. The junction may be disrupted by repeated menstruations and associated myometrial contractions. Pregnancy is another typical example of endometrial–myometrial junction invasion by the trophoblast, supporting the high frequency of adenomyosis among parous women or among those with history of miscarriages [5]. Endometrial traumatization and healing, possibly related to uterine surgery, are also associated with adenomyosis, *via* a tissue-injury and repair (TIAR) mechanism [4].

Pathogenesis of adenomyosis is mainly characterized by estrogen/progesterone imbalance and inflammation, which in turn facilitate the ectopic localization of endometrial cells into the myometrium by disrupting the endometrial–myometrial interface. In particular, an increase of local estrogens in the lesions and reduced progesterone receptor activity within adenomyotic lesions has been observed [6]. Thus, local rather than systemic hyperestrogenism contributes to the development of the disease: a) increased estrogen synthesis (by aromatase); b) reduced estrogens metabolism (by 17ß-hydroxysteroid dehydrogenase type 2 and sulphatase); and c) increased estrogen receptor (ER) activity [6]. Furthermore, some epigenetic aberrations of ER and progesterone receptor (PR) genes may lead to the endocrine-related background, with an hyperestrogenic state enhanced by the lack of progesterone counteracting activity. Specifically, ERβ expression is significantly elevated in adenomyotic glands during the proliferative phase and throughout the myometrium across the menstrual cycle. In addition, while the PR isoform B promoter is hypermethylated with a concomitant PR isoform B downregulation, a PR isoform A dominant state becomes present (progesterone resistance) [7].

Therefore, high local estradiol (E2)-induced hyperperistalsis and microtrauma of JZ contribute to the mechanism of TIAR, promoting a positive feed–forward cycle that facilitates the invasion of the endometrial basalis into the myometrium. The hyperestrogenic *milieu* and progesterone resistance interfere with ectopic endometrial cell proliferation and increased inflammation, facilitating the infiltration of the JZ and the growth of adenomyotic tissue. The overexpression of cyclooxygenases increases the secretion of prostaglandins (PGs), in particular PGE_2, that stimulates aromatase expression, creating a feed-forward loop with estrogens and mediating the mechanisms of adenomyosis-associated pain [4, 6].

Dysregulation of ERs and PRs in adenomyosis also results in aberrant immune cell accumulation and activity, which promote disease development and progression. In fact, macrophages, uterine natural killer cells and T cells are increased in adenomyosis lesions, in an attempt to repair the damage, leading to chronic inflammation and more estrogen production [8].

Furthermore, estrogens contribute to induce a shift of epithelial to mesenchymal markers with the epithelial-mesenchymal transition, thus contributing to fibrogenesis and myometrial smooth muscle proliferation, usually observed in adenomyosis. Besides, estrogen pathway is also implicated in the promotion of neo-angiogenesis mediated by vascular endothelial growth factor [4, 8].

A possible role of oxytocin (OT) has also been suggested, because an increased expression of oxytocin receptors (OTRs) enhances uterine contractility and hyperperistalsis/dysperistalsis, thus contributing to the microtrauma of JZ and the development of adenomyosis. The physiology of uterine contractions is also influenced by prolactin (PRL) and a local overexpression of PRL in the smooth myometrial cells of adenomyosis may facilitate the initiation and progression of the disease [6, 9]. Besides, targeting local PRL or OTRs may be promising in the future for the treatment of this uterine disorder.

A hormonal background of adenomyosis is also supported by the evidence that estrogen-mimetic endocrine disrupting chemicals may promote the development of adenomyosis in animal models. Exposure to dioxin, bisphenol A and phthalates facilitates the disease in rodents, by inducing epigenetic changes in ERs, affecting steroid-sensitive immune-endocrine crosstalk within the uterus [9]. An experimental and clinical evidence for a role of estrogens in adenomyosis is also supported by the observation that tamoxifen, which acts as an estradiol agonist in the uterus, promotes the development of adenomyosis or persistency even in the postmenopause or in animal models [4, 9].

The main clinical proof that adenomyosis is an endocrine-related disorder is the effectiveness of hormonal drugs acting on the hypothalamic-pituitary ovarian (HPO) axis, to manage symptoms, including pain, AUB and fertility-related

issues [10]. The rational of using gonadotropin releasing hormone (GnRH) agonists is based on the suppression of sex steroids hormones, with a direct antiproliferative effect within the myometrium *via* GnRH receptors expressed by adenomyotic lesions, associated to a strong suppression of the HPO axis. A similar effect is observed with oral GnRH antagonists, but their use is still under investigation for adenomyosis. The use of progestins (dienogest, norethindrone acetate, levonorgestrel-releasing intrauterine systems) induce a mild inhibition of ovarian function, with slight hypoestrogenic effects, exerting an antiproliferative action on the endometrium. Progestins act as anti-inflammatory agents, interfering also on neuro-angiogenesis and pain pathways. Despite their limited use, there is also a rationale of prescribing aromatase inhibitors as potential drugs to treat adenomyosis, due to the fact that they interfere with local estrogen production [10].

In conclusion, adenomyosis is a uterine disorder typically observed during female reproductive life. It has been related to an estrogen and progesterone dysfunction, affecting immune function and inflammation, also being linked to an altered effect of OT and PRL on uterine contractility. The hormonal dysfunction in adenomyosis supports the administration of drugs interfering with sex steroid hormones and opens the scenario to the use of additional hormonal treatments based on new pathogenic pathways.

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