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NEW APPROACHES TO THE MANAGEMENT OF WOMEN WITH ENDOMETRIAL HYPERPLASIA

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Abstract: To date, endometrial hyperplasia (hereinafter referred to as EH) is considered the most common disease in gynecology. Timely complex diagnostics of endometrial pathology allows to achieve good results of treatment: stabilization and elimination of pathological foci, thus preserving and restoring reproductive function.

Keywords: Endometrial hyperplasia (EH), endometrial cancer (EC), polycystic ovary syndrome (POS), hormone therapy (HT), progestins, atypical endometrial hyperplasia (AEH), complex non-atypical endometrial hyperplasia (CNAEH), abnormal uterine mottling (AUM), adenocarcinoma.

Introduction Endometrial hyperplasia, in atypical forms, is the precursor lesion for endometrioid adenocarcinoma of the endometrium, representing the most common gynecologic malignancy in industrialized countries.[1] Defined as the disordered proliferation of endometrial glands, endometrial hyperplasia results from estrogenic stimulation of the endometrial tissue with a relative deficiency of progesterone's counterbalancing effects, often referred to in clinical practice as "unopposed."[2] This disordered growth of the endometrium results in an abnormal gland-to-stroma ratio involving varying degrees of histopathological complexity and atypical features in the cells and nuclei. Endometrial hyperplasia, if untreated, has the propensity to develop into endometrial cancer. Strategies for clinical management range from surveillance or progestin therapy to hysterectomy, depending on the risk of progression to or concomitant endometrial cancer and the patient's desire to preserve fertility.[3]The most important risk factor for endometrial hyperplasia and, in turn, endometroid adenocarcinoma is the aforementioned chronic imbalance of or "unopposed" estrogen.[4] The source of exposure to excessive estrogen without the protective effects of progestin can be endogenous, exogenous, or genetic.

Higher estradiol concentrations can be found in obese patients as plasma levels of estradiol-binding sex hormone-binding globulin (SHBG) are typically diminished in this patient population.[5]

Chronic anovulation

When anovulation occurs, sex hormone production is not happening cyclically, and estrogen levels dominate without the opposing effect of progesterone produced by the corpus luteum after ovulation. This imbalance leads to a continued proliferation of the endometrium.[6]

Conditions associated with anovulation include polycystic ovary syndrome (PCOS), hyperprolactinemia, and perimenopausal hormonal status.

Granulosa cell tumors represent potentially estrogen-secreting tumors of the ovary. Accordingly, endometrial hyperplasia is diagnosed in 25% to 50% of women with granulosa cell tumors of the ovary.[7]

Genetic source: Lynch syndrome is a genetic disease of autosomal dominant inheritance caused by mutation of 1 of 4 genes of the DNA mismatch repair system (*MSH2*, *MLH1*, *MSH6*, and *PMS2*), leading to microsatellite instability, which confers a markedly elevated risk for several types of cancers, particularly colon, and endometrial. Patients with hereditary nonpolyposis colorectal cancer have a lifetime risk of 40% to 60% for the development of endometrial cancer.[9] Recent studies have recommended screening patients diagnosed with atypical endometrial hyperplasia or endometrial cancer for microsatellite instability.[10]

EC is the most common gynecologic malignancy in developed countries, the fourth leading cause of cancer, and the sixth cause of cancer death among women.[11] Cancer of the endometrium is rising in the United States, with an estimated incidence of 66,200 cases and 13,030 deaths in 2023.[12] The incidence of EC has increased in many countries over the past few decades, a trend which is hypothesized to be due to the rising prevalence of obesity, as well as shifts towards delaying childbearing.[13] EH is a recognized precursor lesion of the most common type of EC (endometrioid), and its detection offers opportunities for prevention. Prompt diagnosis and treatment can effectively reduce the number of cases of endometrial malignancy.

Estrogenic stimulation of the endometrium, unopposed by progestins, causes proliferative glandular epithelial changes or hyperplasia. Endometrial hyperplasia

results from estrogen predominance and relative progesterone insufficiency. The typical causes for endogenous estrogen excess include anovulatory cycles (perimenopause, PCOS, obesity, and estrogen-secreting ovarian tumors). The exogenous causes include unopposed estrogen therapy, hormone replacement therapy, and tamoxifen (utilized in breast cancer treatment).[2] Hyperplasia, due to prolonged exposure to estrogens, is biologically distinct from the precancerous lesion—atypical endometrial hyperplasia.

This clinical management of the 2 conditions differs depending on the presence or absence of nuclear atypia. Nuclear atypia is defined as nuclear enlargement with or without prominent nucleoli.[14] Endometrial hyperplasia without atypia is a benign lesion without significant somatic genetic changes, caused by extensive exposure to estrogen that is not counterbalanced by the protective effects of progestins. The hyperplastic changes often regress if physiological progesterone levels are resumed or therapeutic progestins are utilized.[15] Endometrial hyperplasia without atypia rarely progresses to endometrial cancer.

On the molecular level, atypical endometrial hyperplasia shares many similarities with **endometrioid** endometrial cancer.[16] Studies have documented a risk of as high as 50% for concomitant endometrial cancer in patients with atypical endometrial hyperplasia.

The risk for the development of endometrial cancer in women with atypical endometrial hyperplasia is diminished approximately threefold to fivefold when treated with progestin. Additionally, when considering the concurrent or future risk of endometrial cancer among women with atypical endometrial hyperplasia, clinicians must understand that atypical endometrial hyperplasia/endometrial intraepithelial neoplasia may be difficult to histopathologically from endometrial cancer. Trimble et al found overdiagnosis or underdiagnosis in nearly every third endometrial specimen, which illustrates the difficulty of this distinction.[17] This challenge suggests that treating atypical endometrial hyperplasia as the equivalent of early endometrial cancer when counseling affected patients is reasonable.

Most patients who receive a diagnosis of endometrial hyperplasia present with abnormal uterine bleeding (eg, abnormal postmenopausal bleeding, persistent or recurrent uterine bleeding).[4] This symptom prompts most patients to seek medical attention almost immediately, contributing to the detection of endometrial cancer at an early stage and, in turn, its relatively favorable prognosis (80%-90% 5-year

survival rate at stage I) when diagnosed and treated.[18] This favorable outcome stands in contrast to other cancers, such as ovarian cancer, whose symptoms are more vague and can remain indolent for many years, allowing it to progress and metastasize.

As with any patient, medical and surgical history should be taken in detail as they may determine contraindications to hormonal treatment or a patient's candidacy for surgery. For instance, a patient with uncontrolled cardiopulmonary disease may have to undergo medical optimization before surgery or may attempt medical management first. Similarly, a patient with a history of breast cancer or liver disease is not a candidate for oral progestins.[19]

The physical examination should include a general routine examination, including vital signs. If a patient is hypotensive, tachycardic, and actively bleeding, she may need fluid resuscitation or a blood transfusion. As most patients present with menorrhagia, pallor should be assessed, which may suggest anemia. A breast examination should be performed to rule out any suspicious lesions, and in women of the appropriate age, normal mammography results within the last year should be confirmed. Most importantly, a pelvic exam should be performed. A speculum should be placed to visualize the quantity of bleeding, flow, and presence of clots. A foul-smelling discharge may suggest active infection and pose a contraindication to potential intrauterine device (IUD) placement. A bimanual exam can ascertain the size of the uterus and the presence of coexisting fibroids or adnexal masses. During the pelvic exam, an endometrial biopsy can be performed to confirm the diagnosis.[20]

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