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Revolutionizing Endometrial Cancer Treatment: Harnessing Hormone Therapy's Potential

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ABSTRACT

In this review paper, various aspects of endometrial cancer, including its diagnosis, stages, treatment options, and associated risk factors. It also distinguishes between Type I and Type II endometrial cancers, highlighting their differences in terms of biology and histopathology. Furthermore, it mentions the role of hormones, particularly estrogen and progesterone, in the development of endometrial cancer and how the use of progestins can mitigate the risk. Additionally, the paragraph touches on the hereditary aspect of endometrial cancer and its association with Lynch syndrome. It concludes by describing the characteristics of Type II endometrial cancer, which tends to affect older postmenopausal women and has distinct histological features and poor prognosis.

INTRODUCTION

Endometrial cancer is often diagnosed at an early stage, due in large part to the symptomatic nature of the disease which presents with uterine/vaginal bleeding.[4] Endometrial cancer, a hormone-dependent malignancy, predominantly presents as endometrial hyperplasia, with subtypes with varying natural histories. The relationship between hormone response, histology, and molecular profile is not well understood.[3] Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program demonstrated that 73% of endometrial cancer patients have stage I disease at diagnosis, whereas approximately 10% are diagnosed with stage II disease The 5-year survival for stage I patients is 85%–91%. 1,2 Most patients are treated surgically and, based on specific pathologic and patient criteria (age, grade of tumor, depth of invasion, presence of lymphovascular space invasion), the patient may be treated with radiation therapy after surgery. Advanced stage (stage III–IV) endometrial cancer is less occasionally, the disease is found outside the abdomen Patients with advanced endometrial cancer are usually treated with surgical debulking followed by radiation, chemotherapy, or a combination thereof. [4] Endometrial cancer is typically diagnosed at stage I, with traditional treatment involving hysterectomy, salpingo-oophorectomy, and pelvic lymph node dissection, followed by adjuvant therapy based on final histology.[1]The study highlights the importance of hormone therapy in the endometrium, highlighting the deregulations in the steroid receptor signaling pathway and their significance in hormone therapy.[2] Recognized as a hormonally responsive tumor, several risk factors have been identified that support a central causal role in endometrial cancers for both estrogen and progesterone. Many of these risk factors provide support for an etiologic hypothesis, known as the unopposed estrogen hypothesis, based on observations that exposure of the endometrium to estrogen without concomitant progesterone can stimulate endometrial cell proliferation that can increase the likelihood of genetic errors and malignant transformation Increased risks of endometrial cancer can result from either excessive estrogen or a progesterone deficiency Several of the major risk factors for endometrial cancer, notably early ages at menarche, late ages at menopause and obesity, provide strong support for the unopposed estrogen hypothesis became commonplace for estrogens to be prescribed in conjunction with a progestin, i.e., as estrogen plus progestin therapy (EPT)—particularly for women with intact uteri. This was found to offer a benefit over unopposed estrogen therapy with respect to the development of endometrial hyperplasia. Thus, most of the recent epidemiologic studies on the effects of menopausal hormones on

endometrial cancer risk have focused on the relative risks and benefits of prescribing progestins, either continuously (usually defined as ≥25 days/month) or sequentially (usually defined as 25 days).[5]

Endometrial Cancer

Type I and Type II endometrial cancer

Types I and II of endometrial cancers have distinct biologic and histopathologic differences.

The Danish Cancer Register was used to identify primary invasive endometrial cancers, using the "International Classification of Diseases for Oncology" C54.0–C55.9 and morphology codes ending with "3." The tumors have been classified as Type I or Type II, except C55.9. Type I tumors included endometrioid , tubular adenocarcinoma, papillary adenocarcinoma, squamous adenocarcinoma, mucinous adenocarcinoma, and adenocarcinoma not otherwise specified. Type II tension and diabetes. The crude models included hormone exposure, age and calendar year. The completely adjusted model also considered hypertension, diabetes, parity, and education. The reference group was women who had never used any hormones.

Type I endometrial count for more than 80% of cases with favorable outcomes, and Are often related to unopposed estrogen or hyperestrogenic environments; they're commonly an endometrioid type. The severity may be initiated from endometrial hyperplasia with out atypia and upgraded to an extra intense status; For example, Endometrial cancer (Grade 1) or complex endometrial hyperplasia with atypia (atypical complex hyperplasia, ACH) Exogenous sources of unopposed estrogen exposure include hormone replacement therapy. therapy (HRT) in postmenopausal women or endogenous, such as obesity or anovulation status. Type I endometrial cancer is the most common extracolonic malignancy if endometrial carcinomas occur in familial penetration (approximately 2e5% Of all endometrial cancers in Western countries) in multiorgan most cancers syndrome, including hereditary nonpolyposis colorectal carcinoma (HNPCC)/Lynch syndrome; the lifetime risk of endometrial cancer varies between 32% and 60% in Lynch syndrome compared with 1% in the general population.

Type II endometrial cancers is regularly associated with age.For example, it regularly takes place in older postmenopausal women, without dependence on estrogen stimulation, and regularly arises in an atrophic environment. The histology includes papillary serous, clear cell, and poorly differentiated carcinomas with a tendency to invade The lymphatic and

vascular spaces, metastasize to lymph nodes, and microscopically contain different intraperitoneal systems regardless of minimalor no invasion within the uterine cavity, and leading to advanced stage, high recurrence rates, and a poor Immunohistochemical staining is often positive for p53 mutations (90%), E-cadherin alteration (approximately 80e90%), and HER-2/neu overexpression (approximately 45e80%), and of most importance, is frequently negative for hormone receptors, such as ERs or PRs. [7,8]

Stage 1: minimal disease is characterized by isolated implants and no significant adhesions.

Stage 2: mild disease, superficial implants that are less than 5cm in total aggregates and scattered over the peritoneum or the ovary.

Stage 3: moderate disease, multiple implants, both superficial and deep +/- presence of adhesions around the tubes or ovaries.

Stage 4: severe disease, multiple superficial and deep implants including large ovarian endometrioma, dense bowel/bladder/ureteric adhesions.

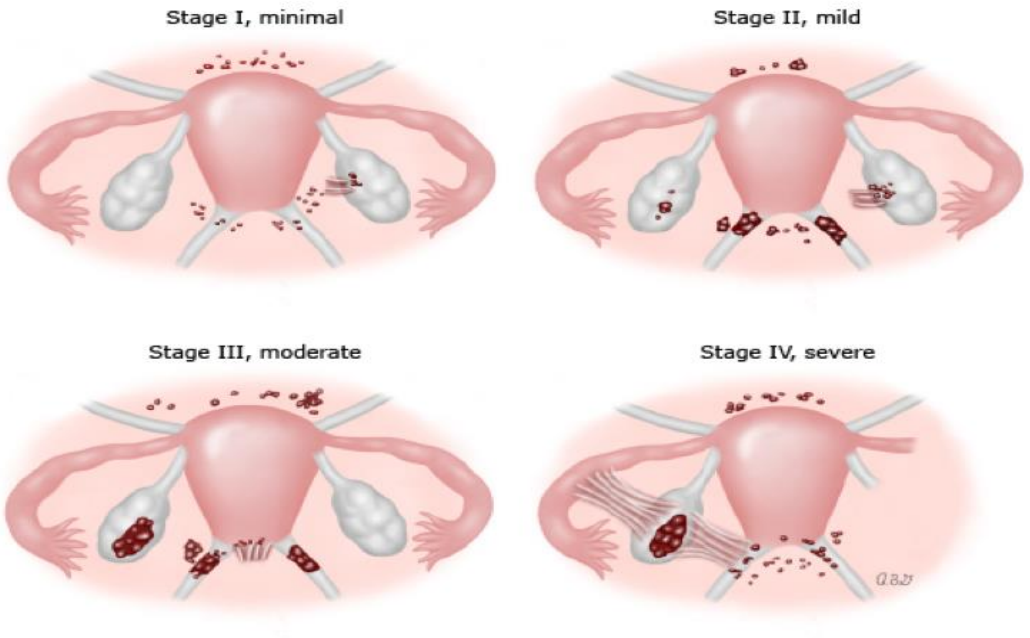

Fig.: Stages of endometriosis

❖ **Epidemiology**

Epidemiology and risk factors

Endometrial adenocarcinoma accounts for 50,000 deaths worldwide(1) and is the most common gynecological cancer in North America, where the incidence is highest (22.0 per 100,000 per year). The disease occurs predominantly in postmenopausal women with a peak incidence around 65–75 years, although 25% of patients occur before menopause and 5% of patients present aged 40 years or less. The wide variation in incidence is attributed to differences in risk factors, which include prolonged exposure to endogenous or exogenous estrogens, obesity, and diabetes mellitus. Adjuvant tamoxifen given for breast cancer is associated with an increased risk of endometrial cancer, as are patients with hereditary nonpolyposis colorectal cancer (HNPCC), a genetic condition associated with DNA repair defects in the enzymes MSH2, MSH6, and hMLH1. Epigenetic inactivation of hMLH1 has also been shown to occur in the 20% of sporadic colorectal and endometrial cancers demonstrating microsatellite instability[18] EC development is primarily linked to estrogen exposure, including medication, nulliparity, early menarche, late menopause, and obesity, which convert androgen into estrogen through aromatase-dependent conversion. [13] Several reproductive elements had been continuously related to the chance for endometriosis (Table 1), suggesting that hormonal variation may have a significant impact on the risk of developing endometriosis. For instance, early age at menarche and short menstrual cycle length are associated with an increased risk, while parity and current oral contraceptive use are associated with a decreased risk. Circulating estradiol and estrone, which stimulate ectopic and eutopic endometrial tissue, are higher among women at an earlier age of menarche and in nulliparous women. Though not a reproductive risk factor, a consistent inverse association has also been observed between body mass index (BMI) and endometriosis and may also relate to hormonal differences between heavy and lean women. [20]No one factor is responsible for all cases of endometriosis, and the disease likely has a multifaceted etiology. One of the earliest and most widely accepted explanations is Sampson's theory of retrograde menstruation.8 This classic theory proposes that, during menstruation, sloughed-off endometrial tissue is refluxed from the uterus through the fallopian tubes. These cells are able to implanting and develop out of doors the uterus inside the pelvic organs and lining or greater remote sites. However, Sampson's principle gives best a partial cause of the etiology of endometriosis. [21]The endometrium is a hormone-responsive tissue and proliferates in response to estrogen exposure, while endometrial growth

is arrested by progesterone in the normal menstrual cycle. Overexposure to estrogen, given either for therapeutic indications or for steroid conversion by adipocytes in obesity, predisposes to hyperplasia of the endometrium, which in a proportion of cases progresses to carcinoma.[18]

❖ Symptoms

Abnormal uterine bleeding is the most common symptom of endometrial cancer, but it can also be caused by other disorders. Postmenopausal women with vaginal bleeding and risk factors for endometrial cancer or hyperplasia should undergo further diagnostic endometrial assessment. The probability of endometrial cancer increases with age and risk factors.[3] Chronic pelvic pain, dysmenorrhea, deep dyspareunia, cyclical bowel or bladder symptoms, subfertility, chronic fatigue, and low back pain are also some additional symptoms symptoms.[15]

❖ Diagnosis

Before addressing the subject on using hormones inside the control of recurrent endometrialmost cancers, clarifying the difficulty of a way to diagnose recurrent endometrial most cancers is of paramount importance. Endometrial cancer recurrence rates range from 7.7% to 19%, with most recurrences detected within 3 years. Tests used in follow-up programs include physical examination, vaginal vault cytology, chest X-ray, abdominal pelvic ultrasound, abdominal pelvic computed tomography, and CA 125. However, recurrences detected during these tests are of low value and should not be used without new evidence. Primary treatment, often through complete staging surgery, usually cures most patients. Postoperative adjuvant therapy, such as radiation, may be arranged for patients at higher risk for recurrence. The salvage rate among recurrent patients varies from 10% to 38%. The majority of remoted vaginal recurrences in girls with surgical Stage I endometrial cancers can be successfully salvaged with radiation therapy, with a 5-year overall survival rate of nearly 75%. Patients with distant recurrence generally have poor prognosis and are often treated systemically, including chemotherapy and hormone therapy, with hormone therapy with progestins being a favored option due to its minimal toxicity. [9] Endometriosis is typically diagnosed through clinical history and physical examination, with palpation for tenderness, retroverted fixtures, nodulating ligaments, and pelvic masses. Pelvic pain is a common symptom of other diseases, so differential diagnosis is crucial. Other tests include

urinalysis, Pap smear, pregnancy test, and vaginal and endocervical swabs. Pelvic ultrasound scans are used to diagnose endometrioma, fibroids, and ovarian cysts. Transvaginal and transabdominal ultrasounds are used to visualize endometrium and uterine cavity but do not rule out peritoneal endometriosis, endometriosis-associated adhesions, and deep infiltrating endometriosis. Magnetic resonance imaging and computed tomography scans are sometimes used to characterize pelvic masses. Laparoscopic inspection with histological confirmation after biopsy is the gold standard for confirmatory diagnosis.[20] Endometriosis diagnosis is challenging due to its multiple causes and potential mimicry of other disorders. During a physical examination, physicians may detect positive signs like tender masses or nodules, but these are not specific or diagnostic. Currently, no simple noninvasive technique is available for diagnosing this disease.[21]

❖ Treatment

The German Society of Senology recommends treatment with selective serotonin-reuptake inhibitors (SSRIs) after breast cancer, which have shown positive efficacy against hot flushes. Other non-hormonal alternatives include methyldopa, clonidine, veralipride, lipophilic beta-blockers, tranquilizers, and vitamin E. However, these substances have shown less efficacy in clinical practice. SSRIs are currently the most effective alternatives, but they can have side effects like nausea, constipation, dry mouth, central nervous system effects, and gastrointestinal bleeding. There have been reports of an increased risk of suicide due to the rapid elimination rate in some patients. SSRIs may be prescribed after breast cancer, but only when the patient refuses HT after informed consent.[6]

Herbal compounds like phytoestrogens and dietary supplements are growing in importance, but the risk of endometrial hyperplasia or ECa cannot be excluded. Hormone-dependent neoplasias are listed as contraindications for many of these products. The compositions of phytopreparations, such as soya, isoflavonoids, red clover, Cimifuga extract, agnus castus, and St John's wort, are complex and only partly known. The actions of the active ingredient have also been little investigated, making it difficult to determine their side effects. [6]

❖ Hormone Therapy

Hormonal therapy is suitable for endometrioid histologies and is particularly effective in asymptomatic patients. For metastatic disease, progestational agents are typically used, but tamoxifen and aromatase inhibitors may also be effective. No specific drug, dose, or schedule

is superior. Response to treatment depends on well-differentiated tumors, a long disease-free interval, and the location and extent of extrapelvic metastases. Progestational therapy is most active among patients with well-differentiated histology and positive progesterone receptor status. The overall response rate ranges from 15% to 25%, with no evidence that higher doses yield better results. However, response to progestational agents is usually short-duration, with a median follow-up period of 2 to 3 months and overall survival of less than a year. [12] A study found that maintenance treatment with low-dose cyclic progestin or a progestin-releasing intrauterine device significantly reduces recurrence after achieving complete response to progestin treatment. This treatment is recommended for patients with superficial myometrial invasion who have achieved a complete response to progestin treatment. A study of 14 patients with stage IA, grade 2-3 differentiation without myometrial invasion found that 70% had a complete response, and 30% had recurrent disease. However, no literature exists for patients with superficial myometrial invasion or grade 1 differentiation.[10]

This randomized prospective multi-institutional study demonstrates that CAF therapy combined with cyclical Provera-Tamoxifen may be more effective in treating metastatic or recurrent endometrial adenocarcinoma than CAF therapy alone. The beneficial effect of cyclical hormonal therapy can be explained by the concomitant ER and PR concentration results in localized operable disease. Patients with negative ER have more undifferentiated neoplasms and a higher tendency to relapse, which can be significantly diminished by adjuvant cyclical hormonal therapy. The prognostic value of ER and PR measurements and the role of hormonal therapy is now better appreciated. Negative PR levels in anaplastic carcinomas have been reported by many investigators, but only 15% of such tumors respond to progestins. Recently, it was shown that ER status is an important prognostic factor in patients with endometrial cancer. Combining chemotherapy and progestins has been reported by many cooperative groups with slightly superior results. The study found that chemo-hormonal therapy showed a significantly better response rate with a 26% complete remission rate for a period of more than 38 months. The administration of palliative radiotherapy was a factor that probably helped in obtaining these results. The sequential cyclical schedule of Provera followed by TAM stems from Mortel's hypothesis, which postulates that TAM may increase the degree and duration of response of endometrial carcinoma to progestin therapy.[11] A survey of UK consultant gynecologists revealed that oral progestins and the levonorgestrel intrauterine system (LNG-IUS) are the most popular conservative treatment options for complex endometrial hyperplasia. However, over 80% of gynecologists would

perform a hysterectomy for ACH, only considering LNG-IUS or oral progestins as a secondary option. More gynecologists favor LNG-IUS as a secondary choice.[7] Endometriosis is sensitive to estrogen, as it is rare before puberty or after menopause, typically results in regression after surgical removal of both ovaries, can be regressed with a gonadotropin-releasing hormone agonist, and can develop in the prostatic utricle of men treated with diethylstilbestrol for prostate cancer.[17]

- **Hormones used during hormone therapy**

➢ Progesterones/progestins

Progesterone became determined in 1933. Its consequences are mediated via interaction with the PR, a transcription factor, and a member Of a big family of structurally associated gene product referred to as the nuclear receptor superfamily. PRA and PRB are two isoforms of the PR gene, with distinct roles in endometrial development. Altering PR expression can lead to hyperplasia or tumor formation. Estrogeneprogestin therapy, which adds synthetic progestin, prevents endometrial cancer development and may decrease the risk, suggesting progesterone's role in endometrial differentiation and carcinogenesis. [9] Progestogens were initially used in unselected patient populations due to their lack of side effects compared to cytotoxic chemotherapy but now are confined to better-differentiated cases with estrogen and progesterone receptors.[18] Progesterone, a class of agents, has been found to control cellular proliferation, induce differentiation, and interfere with the invasive potential of endometrial cells, though its exact mechanisms remain unknown.[16]

➢ Some modifications of progestins

Tamoxifen may prevent PR downregulation and improve response duration, impacting median progression-free and overall survival in advanced endometrial cancer. A study randomized patients to MA or tamoxifen therapy, finding no clinical advantages. However, a Phase II study showed a 33% response rate with a median 3-month progression-free survival and 13-month overall survival. Another study found a 27% response rate with a response duration of over 20 months. The relationship between estrogen receptor (ER) and progesterone (PR) was found to be significantly related to clinical response to daily tamoxifen and intermittent weekly MPA.[9] Therapeutic hormones like progestational agents and tamoxifen have been used in various cancer treatments. Tamoxifen, an antiestrogen, was

identified as a therapeutic agent in endometrial cancer in the 1980s, highlighting the complexities of tissue-hormonal interactions in the endometrium.[18]

➢ Other hormones

Tamoxifen, a selective ER modulator, has been shown to have diverse effects on endometrial cancer pathogenesis due to its potential therapeutic effects and potential risk of inducing the formation of endometrial cancer. Studies have shown a response rate of 10% in advanced or recurrent endometrial cancer, 1.9-month median progression-free survival, and 8.8-month median in general survival. Combining tamoxifen and MPA therapy has shown promising results, with a 2.7-month median progression-free survival and 14-month overall survival. Arzoxifene, a modification of raloxifene, has shown a 31% response rate in hormone-receptor-positive or well-differentiated endometrial cancer, with a median response of 13.9 months.[18]

- **CURRENT HORMONAL DRUG USED**

➢ Combined hormonal contraceptives

Endometriosis is a reproductive disorder that requires effective contraception to prevent unintended pregnancies and treat the disease. Combined hormonal contraceptives (CHCs) play a crucial role in preventing ovulation by inhibiting follicular development, ovulation, and corpus luteum formation. The progestin component of CHCs is particularly effective in ovulation inhibition. The history of CHCs dates back to about 60 years, with the first combined oral contraceptive (COC) approved around 60 years ago. The evolution of CHCs has included the use of synthetic estrogens, progestins, and parenteral administration methods. The European Society of Human Reproduction and Embryology (ESHRE) guidelines classify COCs as Grade B for reducing endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain. CHCs have shown good tolerability and low costs, with a recent systematic review showing significant reductions in endometriosis-related pain and QoL. However, data supporting CHC use in endometriosis patients is often low quality due to nonrandom allocation of treatments, treatment concealment, and lack of a placebo arm.[19]

➢ Progestins

Progestins are synthetic steroids with similar actions to natural progesterone, primarily acting on the P-receptor (PR). The affinity for PR varies significantly between progestins, with two predominant isoforms in women being PR-A and PR-B. Progestins interact with various nuclear receptors, including androgen, glucocorticoid, and mineralocorticoid receptors, leading to agonistic or antagonistic actions. Endometriosis treatment is a primary indication for progestins, with the European Society of Human Reproduction and Embryology (ESHRE) classifying them for endometriosis-related pain. Progestins can be administered orally, subdermally, intramuscularly, or intrauterine systems. Some formulations are globally approved as hormonal contraceptives, such as oral DSG, etonogestrel implants, MPA depot injections, and levonorgestrel-containing IUS (LNG-IUS). However, progestins have fewer contraindications due to lower thrombotic risk compared to contraceptives like CHCs. Progesterone resistance in patients refractory to hormonal therapies may be due to imbalances in estrogen and progestin receptor subtypes or adhesion molecules.[19] Progestins have been used for palliative endometrial cancer treatment for decades, with response rates ranging from 30-50%. Recent studies show objective response rates of 10%-25%, with response rates of 26% and 18%, suggesting that high doses of medroxyprogesterone acetate (MPA) are not superior.[14]

- Gonadotropin releasing hormone agonists

Other hormonal agents have been explored for a role in the management of metastatic or recurrent endometrial cancer. Of potential interest, it has been shown that a high percentage of endometrial cancer cells possess receptors for gonadotropin-releasing hormone, including high-grade cancers.[16] GnRH antagonists, decapeptides that differ from the endogenous GnRH, are second-line therapy for endometriosis. These drugs suppress estrogen ovarian production by down-regulating GnRH receptors at the pituitary level, decreasing levels of LH and FSH. However, GnRH-as can cause several adverse effects (AEs), such as lipid profile alteration, flushes, depression, urogenital atrophying, and loss of BMD. To decrease these AEs, appropriate "add-back" treatments should be started within 6 months of the beginning of GnRH-agonist administration. A systematic review by Cochrane evaluated the use of GnRH-agonists for pain symptoms associated with endometriosis, finding them more efficacious in relieving pain symptoms compared to no treatment or placebo. Several trials compared GnRH-agonists with no treatment or placebo, finding significant benefits in pain relief and overall resolution of symptoms. GnRH agonists have been compared to almost all available hormonal treatments commonly used for the treatment of endometriosis-associated pain.[19]

➢ Aromatase inhibitors

Since the late 1990s, laboratory studies have shown that aromatase P450, responsible for the conversion of androstenedione and testosterone to estrone, is expressed in both eutopic and ectopic endometrium of women with endometriosis. This has led to the investigation of third-generation nonsteroidal aromatase inhibitors (AIs), such as letrozole (LTZ) and anastrozole, for treating endometriosis. A systematic review of ten clinical studies identified that continuous administration of LTZ and anastrozole reduced pain symptoms and improved women's quality of life. However, current data shows limited use of AIs due to AEs such as bone and joint pain, muscle aches, and fatigue. AIs should be administered together with COCs, progestins, or GnRH-agonists. The ESHRE guidelines currently recommend AIs in combination with COCs, progestins, or GnRH-agonists in women with rectovaginal endometriosis, refractory to other medical or surgical treatments. LTZ has been the most investigated drug for treating endometriosis, with a randomized prospective open-label study showing significant reductions in chronic pelvic pain and deep dyspareunia after 3 and 6 months of treatment.[19]

❖ Conclusion

Endometrial cancer is a growing health concern, and this review explores molecular markers related to chemo- and hormone therapy resistance. The review delves into the complex mechanisms and potential targets for better treatment outcomes, emphasizing the importance of personalized approaches. As research progresses, identifying these markers and innovative strategies promises to enhance endometrial cancer management and patient outcomes.

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