Endometrial Hyperplasia — Diagnosis and Treatment

Endometrial hyperplasia is abnormal growth of the endometrium in the uterus. It is caused by excess estrogen unopposed by progesterone. Pathology shows an increased gland-to-stroma ratio and can show atypia. Atypia is linked to endometrial cancer, the most common gynecological malignancy in the developed world. Treatment includes progesterone therapy and if there is atypia hysterectomy is recommended. Lynch syndrome has a high lifetime risk of developing endometrial cancer.

Definition and Epidemiology of Endometrial Hyperplasia

Endometrial hyperplasia is an increase in the number of cells in the endometrium of the uterus. The endometrium is the innermost layer of the uterus with the other layers that follow being the myometrium and perimetrium. In some cases it is associated with malignancy.

Endometrial hyperplasia has an incidence of 133 women per 100,000 per year. With most cases occurring in the postmenopausal years 50 to 54. Atypical hyperplasia is seen most commonly in 60 to 64 year olds. It is suggested that many women do not
report to their doctor when they are symptomatic or they report after the hyperplasia remits so the estimates of incidence are more than likely low.

While endometrial hyperplasia occurs the most in postmenopausal women, it can occur at much younger ages where estrogen is unopposed as seen in polycystic ovarian syndrome and obesity.

In some cases of endometrial hyperplasia, especially with atypical, it can progress to endometrial cancer and it is important to study these together. Endometrial cancer is the most common gynecological cancer in the developed world and the second most in the developing world.

USMLE Pearl: It is important to know the list of most common cancers in men and women. For gynecological cancers, cervical cancer is the most common in developing countries due to a lack of screening and HPV vaccine. There are 25.4 new cases per 100,000 women per year. Deaths are 4.5 per 100,000 women per year. Women have a lifetime risk of 2.8%. The average age of diagnosis is between 55 and 67. Only 5% of cases occur in women under the age of 40.

It is important to be aware of the genetic disease known as Lynch syndrome which has a 22-50% lifetime risk of developing endometrial cancer.

Etiology of Endometrial Hyperplasia

The basic principle to understand is that there is an increase in estrogen which is unopposed by progesterone leading to proliferation of endometrial tissue.

Some important risk factors to be aware of are polycystic ovary syndrome, obesity, nulliparity, early menarche, and late menopause.

Obesity increases the risk because there is an excess of estrogen produced from the increased number of adipocytes. Adipocytes have an enzyme called aromatase, which is key in the production of estrogen.

From a genetics standpoint, Lynch syndrome (hereditary nonpolyposis colorectal cancer) is associated with endometrial cancer.

USMLE Pearl: Lynch syndrome has autosomal dominant inheritance. It is caused by mutations in DNA mismatch repair genes that lead to microsatellite instability. Carriers have an almost certain risk of colon cancer and females have a high risk of gynecological cancers.
The **Selective Estrogen Receptor Modulator** (SERM), *tamoxifen*, has been shown to increase your risk due to its estrogen partial agonist effect on the endometrium. A more recent study from SEER has suggested that it does not increase your overall risk.

Although rare, an **estradiol secreting ovarian tumor** can produce endometrial hyperplasia.

**Classification of Endometrial Hyperplasia**

The WHO has two classifications for endometrial hyperplasia:

- **Glandular stromal changes** that are described as simple or complex
- Endometrial hyperplasia with or without atypia.

This results in four categories:

- Simple without atypia
- Complex without atypia
- Simple with atypia
- Complex with atypia

**Simple** is described as a mild increase in gland number that may show **mitosis**.

**Complex** has a great increase in gland-to-stroma ratio greater than 50% with cellular disorganization. Cells usually show mitosis.

**Atypia** will show nuclear enlargement with abnormal chromatin.

**Endometrial carcinoma** is classified into two types based upon histology, progression, incidence, and estrogen sensitivity:

- Type 1: endometrioid adenocarcinoma
- Type 2: serous/clear cell

**Pathophysiology of Endometrial Hyperplasia**

Endometrial hyperplasia is caused by increased amounts of estrogen unopposed by progesterone.

In a normal cycle, estrogen is released from the ovaries, which induces the endometrium to proliferate in preparation for implantation. **Ovulation** causes progesterone to increase, which stabilizes and prepares the endometrium for possible implantation. If no implantation occurs then both estrogen and progesterone levels decrease and **menstruation** occurs.
As a woman ages and reaches perimenopause and menopause, ovulation occurs less or not at all. Due to the lack of ovulation there is a loss of progesterone to counteract remaining estrogen. The estrogen then allows for increased growth of the endometrium. With the increased proliferation, there are risks for abnormal changes in nuclei, atypia. Atypia is associated with a chance up to 60% of having or developing endometrial cancer. In many cases the hyperplasia will regress on its own.

If malignancy develops, most cases will be type 1 endometrioid adenocarcinomas which have a more favorable outcome.

**Signs and Symptoms of Endometrial Hyperplasia**

Abnormal uterine bleeding is the number one most reported sign.

Additional symptoms may include:

- **Menorrhagia**: increased amount of blood loss greater than 80mls or bleeding for longer than 8 days.
- **Menometrorrhagia**: increased irregular bleeding (thought of as a mix of menorrhagia and metrorrhagia)
- **Postmenopausal bleeding**.

**Progression and Special Forms of Endometrial Hyperplasia**

Atypia has the strongest association with progressing to endometrial cancer.

Women with Lynch syndrome need to be screened starting at 35 years old for endometrial cancer since they have a high chance of developing the disease. It is recommended that if the woman is done with family planning to have a hysterectomy with bilateral salpingostomy.

**Diagnosis and Pathology of Endometrial**
Hyperplasia

There is no formal screening method for the general population and screening is usually done when signs or symptoms are present.

The American Congress of Obstetricians and Gynecologists recommends that any woman with abnormal uterine bleeding over the age of 35 be screened for endometrial hyperplasia. Women under the age of 35 who have abnormal uterine bleeding that is not controlled with medication should be screened also.

History and physical exam may help to elucidate the etiology of the bleeding. Physical exam may be grossly normal and show no signs of malignancy.

Initial tests can include transvaginal ultrasound to measure the endometrial thickness and to screen for any other potential causes. If the endometrium is deemed to be thickened, an endometrial biopsy can be performed in the clinic. Other biopsy methods which are in the operating room are dilation and curettage (commonly referred to as a D and C) and hysteroscopy.

Pathology of endometrial hyperplasia

Pathology leads to a definitive diagnosis and is the best way to view changes of the endometrium. In the clinic, a pipelle is used to sample the endometrium.

Type 1 endometrioid makes up 80% of the endometrial cancers and they have a favorable outcome. The histology has an increased gland-to-stroma ratio and can be referred to as adenocarcinoma because of the increased number of glands.

Type 2 serous/clear cell makes up 20%. They have a poorer outcome due to myometrial and extraterine involvement. The histology will depend more on the type of malignant cells seen, but most have an adenocarcinoma or mixed basis.

Mutations are seen in p53, PTEN, PIK3CA, K-Ras, and β-catenin.

Staging for carcinoma is done with the International Federation of Gynecology and Obstetrics (FIGO) or with the TNM scale.
Differential Diagnosis of Endometrial Hyperplasia

Differentials include any cause of abnormal uterine bleeding:

- Trauma
- Neoplasm
- Atrophic vaginitis
- Polyps
- Endometritis
- Salpingitis
- Cervicitis
- Leiomyomas
- Menstruation
- Secondary bleeding due to hormone replacement therapy

Therapy and Prevention of Endometrial Hyperplasia

Therapy depends upon the type of hyperplasia and the patient’s desire for future fertility.

Without atypia there is a 1-3% chance of progressing to endometrial cancer. Progestin therapy is the most accepted method for treatment of endometrial hyperplasia without atypia.

Progestin can be given orally or released from an intramuscular injection or intrauterine device (IUD). First line therapy includes oral medroxyprogesterone. Mixed estrogen-progestin oral contraceptives can be used in some patients. Levonorgestrel IUDs, such as the mirena, have been shown to be very effective in treatment and offer long term contraception.

Endometrial hyperplasia without atypia has a very favorable response with regression occurring within 3-6 months. If after that time regression has not occurred then progestin dose should be increased.
Atypical endometrial hyperplasia has a greater risk of progressing to cancer. If future pregnancy is not desired then **hysterectomy** is a definitive treatment. In postmenopausal women **bilateral salpingo oophorectomy** is recommended.

If pregnancy is desired, then **progestin therapy** is used as surgery, even conservative, will not allow for pregnancy. Progestin can be given orally or released from an **intramuscular injection** or **IUD**. Common oral progestins used are **oral megestrol acetate** and **medroxyprogesterone**.

**Intramuscular Depot medroxyprogesterone (Depo-Provera) injection** four times a year has shown to be effective. IUDs such as mirena can be used as well.

**Biopsies** should be repeated every 6-12 months if continuing with progestin therapy to monitor for progression.

Outcomes are generally good with regression taking on average 6-9 months. Current studies show regression of 86% and a relapse rate of 23-26%.

If there is possible **metastases** the chemotherapy drug **Cisplatin** has been shown to be effective.

**Lymph node metastasis** will go to pelvic or para-aortic nodes. If metastasis has reached these nodes they need to be removed.

Overall with treatment there is a 5-year survival rate of 83% for endometrial cancer.

**Complications of endometrial hyperplasia**

**Hysterectomy** with **bilateral salpingo oophorectomy** in premenopausal women can lead to **early onset menopause** and result in all of the symptoms of menopause and should be treated accordingly.

**Prevention of endometrial hyperplasia**

Women can take the following preventative measures:

- Women who use estrogen should take a **progesterone** to prevent against the unopposed estrogen effect.
- Younger women with irregular menstrual periods should be treated with **oral birth control** that contains both estrogen and progestin in order to help regulate their cycle.
- Maintaining a **healthy BMI** and losing weight if you are overweight or obese.

**Cigarette smoking** has been shown to be protective against endometrial cancer. Due to the negative effects that smoking has on the lungs and other organs it is not recommended.

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