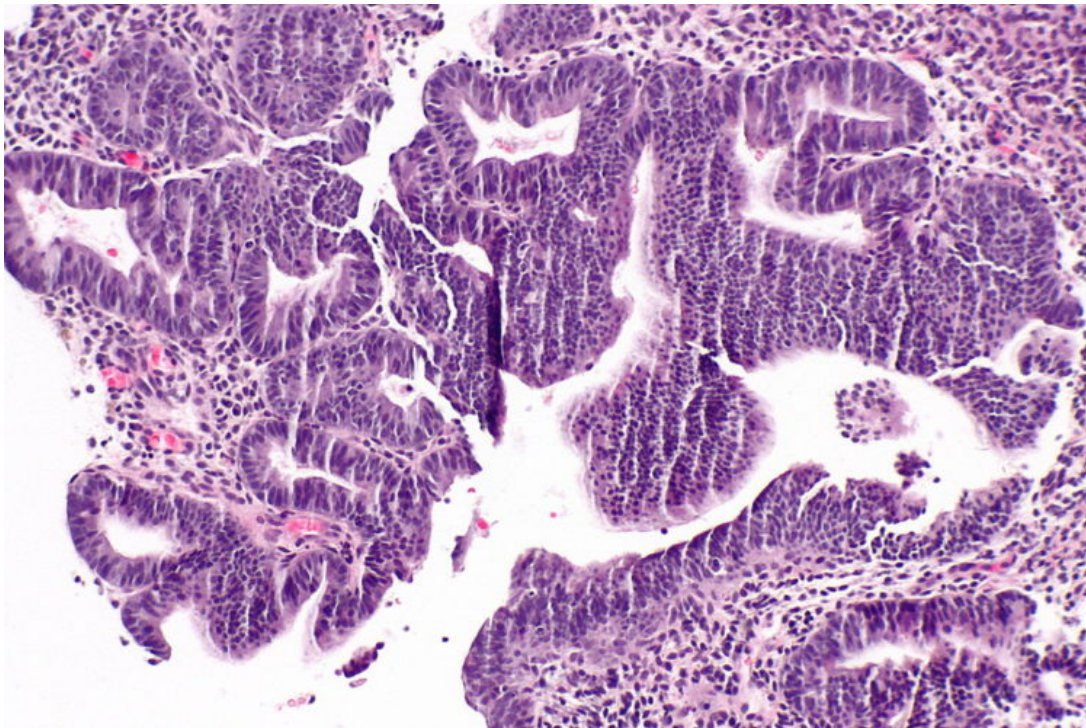


Endometrial Hyperplasia — Diagnosis and Treatment

[See online here](#)

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 atypic hysterectomy is recommended. Lynch syndrome has a high lifetime risk of developing endometrial cancer.



Definition and Epidemiology of Endometrial Hyperplasia

The endometrium is the uterine lining or the innermost layer of the uterus; the other layers are the myometrium and perimetrium. Endometrial hyperplasia is an **abnormal thickening of the endometrium** suspected when the endometrial thickness is ≥ 5 mm in postmenopausal women and > 1 cm in premenopausal women. In some cases, it is associated with malignancy.

The incidence of endometrial hyperplasia is **133 women per 100,000 per year**. Most cases occur after menopause, in women from **50 to 54 years of age**. Atypical

hyperplasia is seen most commonly in 60- to 64-year-olds. Estimates of incidence are believed to be low because many women do not report their symptoms or report only after symptoms remit.

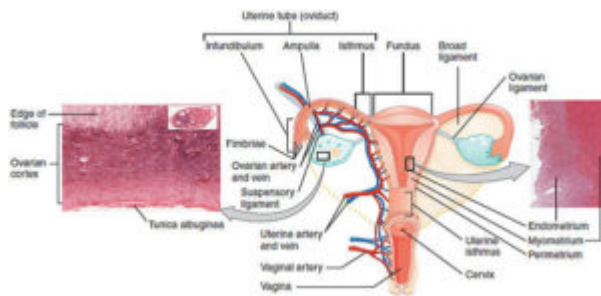


Image: "Illustration of the female reproductive system." by OpenStax College - Anatomy & Physiology, Connexions Web site. <http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22> @6.27:189, Jun 19, 2013. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Although endometrial hyperplasia occurs mostly in postmenopausal women, it can occur at much younger ages when estrogen is unopposed, as seen in **polycystic ovarian syndrome** and **obesity**.

Some cases of endometrial hyperplasia, especially atypical, can progress to **endometrial cancer**, so it is important to study the two together. Endometrial cancer is the most common gynecological cancer in the developed world and the second-most common in the developing world.

Note for the United States Medical Licensing Examination (USMLE): It is important to know the list of the 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 vaccination against human papillomavirus (HPV). There are 25.4 new cases per 100,000 women per year, leading to death in 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 years. Only 5% of cases occur in women younger than 40 years.

Etiology of Endometrial Hyperplasia

The basic principle is that an **increase in estrogen** that is **unopposed by progesterone** leads to a **proliferation of endometrial tissue**.

Some important risk factors are **polycystic ovarian syndrome, obesity, nulliparity, early menarche, and late menopause**.

Obesity increases risk because of an **excess amount of estrogen** produced from the increased number of adipocytes. **Adipocytes** contain an enzyme called **aromatase**, which is crucial for the production of estrogen.

Lynch syndrome (hereditary nonpolyposis **colorectal cancer**) is associated with a 22%–50% lifetime risk of developing into endometrial cancer.

Note for USMLE: Lynch syndrome has an **autosomal dominant inheritance**. It is caused by mutations in DNA mismatch repair genes that lead to microsatellite instability (a repetitive segment of DNA). Carriers have an almost certain risk of colon cancer, and women have a risk of developing gynecological cancers of up to 40%.

Some studies have shown that the **selective estrogen receptor modulator**

tamoxifen increases risk due to its estrogen partial agonist effect on the endometrium. However, a recent study from the Surveillance, Epidemiology, and End Results Program suggested that it does not increase overall risk.

Although rare, **estradiol-secreting ovarian tumors** can produce endometrial hyperplasia.

Classification of Endometrial Hyperplasia

The World Health Organization (WHO) has two classifications for endometrial hyperplasia:

- **Based on the type of glandular stromal changes**, that are described as simple or complex
- **Based on the presence or absence of atypia** (structurally irregular or abnormal cells) in the endometrium

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 an increase in gland-to-stroma ratio greater than 50% with cellular disorganization. Cells usually show mitosis.

Atypia is represented by nuclear enlargement, abnormal chromatin, and polymorphism.

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.

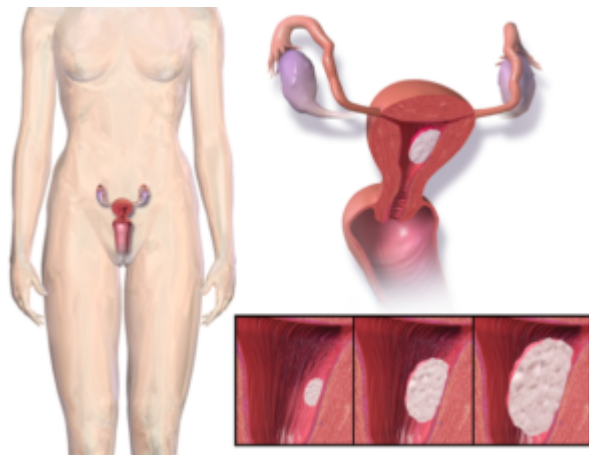


Image: "Illustration of endometrial cancer." by Blausen Medical Communications, Inc. – Donated via OTRS, see ticket for details.
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As a woman ages and reaches **perimenopause** and **menopause**, ovulation occurs less often or not at all. Due to the lack of ovulation, there is a loss of progesterone to counteract remaining estrogen. Estrogen then allows for increased and unopposed growth of the endometrium.

With increased proliferation come risks for **abnormal changes in nuclei**—atypia. **Atypia** is associated with a chance as high as 60% of having or developing **endometrial cancer**. However, in many cases, hyperplasia regresses on its own.

If **malignancy** develops, most cases are **type 1 endometrioid adenocarcinomas**, which have more favorable outcomes.

Signs and Symptoms of Endometrial Hyperplasia

Abnormal uterine bleeding is the most commonly reported sign.

Additional symptoms may include:

- **Menorrhagia:** increased blood loss greater than 80 ml or bleeding that lasts longer than 8 days.
- **Menometrorrhagia:** increased irregular bleeding (thought of as a mix of menorrhagia and metrorrhagia)
- **Postmenopausal bleeding:** any amount of vaginal bleeding, including spotting or staining after a woman had already experienced a cease in menstruation due to menopause

Progression and Special Forms of Endometrial Hyperplasia

Types that present with **atypia** have the strongest association with progression to **endometrial cancer**.

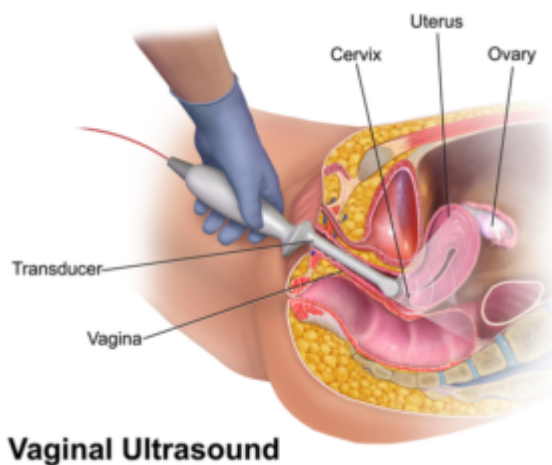
Women with **Lynch syndrome** should be screened for endometrial cancer starting at age 35 because they have a high chance of developing the disease (up to 40%). If a woman has no further plans of having children, **hysterectomy with bilateral salpingectomy** is recommended.

Diagnosis and Pathology of Endometrial Hyperplasia

No formal screening method exists for the general population, so screening usually is done when signs or symptoms are present.

The American Congress of Obstetricians and Gynecologists recommends that any woman who is older than 35 and has **abnormal uterine bleeding** be screened for endometrial hyperplasia. Women younger than 35 who have abnormal uterine bleeding that is not controlled with medication also should be screened.

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



[Image:](#) "Transvaginal ultrasonography procedure." by BruceBlaus. License: [CC BY-SA 4.0](#)

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 (> 5 mm), an **endometrial biopsy** can be performed. Other biopsy methods can be performed in the operating room, including **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 in the endometrium. In the clinic, a **pipelle** is used to sample the endometrial tissue.

Type 1 endometrioid is responsible for 80% of endometrial cancers; fortunately, has a favorable outcome. Histology shows an increased gland-to-stroma ratio and can be referred to as **adenocarcinoma** because of the increased number and size of glands.

Type 2 serous/clear cell is responsible for 20% of endometrial cancers. Such cases have poorer outcomes due to **myometrial and extrauterine involvement**. Histology depends more on the type of malignant cells seen, but most have adenocarcinoma or a mixed basis.

Mutations have been reported in p53, PTEN, PIK3CA, K-Ras, and β -catenin.

Staging for carcinoma is done with the International Federation of Gynecology and Obstetrics (also known as FIGO) staging system or with the TNM (tumor [T], nodes [N], and metastases [M]) scale.

Differential Diagnosis of Endometrial Hyperplasia

Differentials include any cause of abnormal uterine bleeding:

- Abdominal or pelvic trauma, especially those of a sexual nature
- Gynecologic cancer or other cancers metastasizing to the uterus
- Atrophic vaginitis
- Endometrial polyps or fibroids
- Endometritis
- [Salpingitis](#)
- Cervicitis
- Leiomyomas
- Menstruation
- Secondary bleeding due to hormone-replacement therapy
- Pregnancy

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 that hyperplasia will progress to endometrial cancer. **Progestin therapy** is the most accepted method for the treatment of endometrial hyperplasia without atypia.

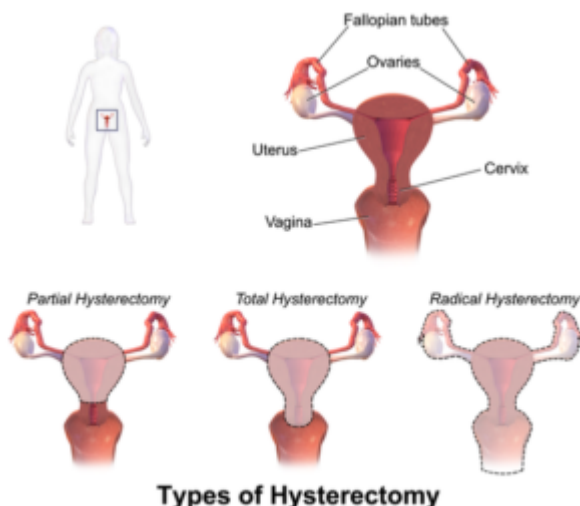


Image: "Types of hysterectomy." by BruceBlaus - Own work.
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Progestin can be given orally or released from an intramuscular injection or intrauterine device (IUD). First-line therapy includes **oral medroxyprogesterone**. Mixed estrogen-progestin oral contraceptives can be used in some patients. **Levonorgestrel IUDs**, such as the Mirena, have been shown to be very effective in the treatment of endometrial hyperplasia and offer long-term contraception.

Endometrial hyperplasia without atypia has very favorable response rates, with regression occurring within three to six months. If after that time regression has not occurred, then progestin dose should be increased.

Endometrial hyperplasia with atypia has a greater risk of progressing to cancer. If future pregnancy is not desired, then **hysterectomy** is the best and definitive treatment. In postmenopausal women, **bilateral salpingo-oophorectomy** is recommended.

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

An **intramuscular depot medroxyprogesterone (Depo-Provera) injection** four times a year has shown to be effective. Again, IUDs such as Mirena can be used as well.

If a patient continues with progestin therapy, a **biopsy** should be repeated every six to 12 months to monitor for progression.

Outcomes are generally good, with regression averaging six to nine months. Current studies show a regression rate of 86% and a relapse rate of 23%–26%.

When **metastases** are possible, chemotherapy drug **cisplatin** has been shown to be effective.

Lymph node metastasis will go to the pelvic or para-aortic nodes. If metastasis reaches these nodes, they must be removed.

Overall, with treatment, patients with endometrial cancer have a 5-year survival rate of 83%.

Complications of Endometrial Hyperplasia

Hysterectomy with **bilateral salpingo-oophorectomy** in premenopausal women will lead to **surgical menopause** and result in all of the symptoms of menopause, which should be treated accordingly.

Prevention of Endometrial Hyperplasia

Women can take the following preventative measures:

- Women who use estrogen should take **progesterone** as well to prevent 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 cycles.
- Women should maintain a **healthy body mass index**; those who are overweight or obese should lose weight accordingly.

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

References

Premalignant lesions of the Endometrium via [medscape.com](#)

Endometrial Carcinoma via [medscape.com](#)

[Classification and diagnosis of endometrial hyperplasia](#) via [uptodate.com](#)

[Endometrial Carcinoma: Clinical features and diagnosis](#) via [uptodate.com](#)

[SEER stat fact sheets: endometrial cancer](#) via [seer.cancer.gov](#)

[Endometrial Hyperplasia](#) via [acog.org](#)

[Endometrial Cancer](#) via [acog.org](#)

REED, Susan D. et al. "Incidence of Endometrial Hyperplasia." American journal of obstetrics and gynecology 200.6 (2009): 678.e1-678.e6. PMC. Web. 17 Nov. 2016.

Emons, G. et al. "New WHO Classification of Endometrial Hyperplasias." Geburtshilfe und Frauenheilkunde 75.2 (2015): 135-136. PMC. Web. 16 Nov. 2016.

Colombo, N; Preti, E; Landoni, F; Carinelli, S; Colombo, A; Marini, C; Sessa, C (2011). "Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". Annals of Oncology. 22 (Supplement 6): vi35-vi39.

Abu Hashim, Hatem et al. Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials. American Journal of Obstetrics & Gynecology , 2015, Volume 213 , Issue 4 , 469 - 478

Le , Tao and Bhushan , Vikas. First Aid for the USMLE Step 1 2014. New York: McGraw-Hill Education, 2014.

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