ENDOMETRIAL HYPERPLASIA

Endometrial Overgrowth, Eh

Thickening of the lining of the uterus.

♀ Diagnosis  ♂ Female

**Related Diagnoses:**

Obesity | Polycystic ovary syndrome | Endometriosis | Thyroid disorders | Endometrial cancer | Amenorrhoea | Oligomenorrhea

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### About Endometrial hyperplasia

Endometrial hyperplasia is a condition of excessive proliferation of the cells of the endometrium, or inner lining of the uterus.

Most cases of endometrial hyperplasia result from high levels of estrogens, combined with insufficient levels of the progesterone-like hormones which ordinarily counteract estrogen's proliferative effects on this tissue. This may occur in a number of settings, including obesity, polycystic ovary syndrome, estrogen producing tumours (e.g. granulosa cell tumour) and certain formulations of estrogen replacement therapy. Endometrial hyperplasia is a significant risk factor for the development or even co-existence of endometrial cancer, so careful monitoring and treatment of women with this disorder is essential.

Like other hyperplastic disorders, endometrial hyperplasia initially represents a physiological response of endometrial tissue to the growth-promoting actions of estrogen. However, the gland-forming cells of a hyperplastic endometrium may also undergo changes over time which predispose them to cancerous transformation. Several histopathology subtypes of endometrial hyperplasia are recognizable to the pathologist, with different therapeutic and prognostic implications.

Two different systems are commonly used to classify EH, the World Health Organization (WHO) and the endometrial intraepithelial neoplasia (EIN) (Tab. 1). The WHO classification system, which is the most commonly recognized system, use cellular complexity, crowding of the endometrial gland and the presence of cytological atypia to categorize pathologies as simple or complex hyperplasia, with or without atypia. The complexity of the WHO classification system has prompted improvement of an alternative system, the EIN. The EIN classifies EH as either benign or hyperplasia, and includes additional EIN and cancer classifications. Cases are categorized as EIN based on architectural gland crowding, altered cytology and maximum linear dimension of the lesion exceeding 1 mm, while excluding cancer and mimics. The EIN classification system can easily be applied to routine H&E stained sections and is more reproducible, helping clinicians to select treatment options.

However, the most commonly used classification system for endometrial hyperplasia is the World Health Organization system, which has four categories:

1. simple hyperplasia without atypia
2. complex hyperplasia without atypia
3. simple atypical hyperplasia
4. complex atypical hyperplasia

(1. + 2.) Endometrial hyperplasia (simple or complex) - Irregularity and cystic expansion of glands (simple) or crowding and budding of glands (complex) without worrisome changes in the appearance of individual gland cells. In one study, 1.6% of patients diagnosed with these abnormalities eventually developed endometrial cancer.
Atypical endometrial hyperplasia (simple or complex) - Simple or complex architectural changes, with worrisome (atypical) changes in gland cells, including cell stratification, tufting, loss of nuclear polarity, enlarged nuclei, and an increase in mitotic activity. These changes are similar to those seen in true cancer cells, but atypical hyperplasia does not show invasion into the connective tissues, the defining characteristic of cancer. The previously mentioned study found that 22% of patients with atypical hyperplasia eventually developed cancer.

Diagnosis of endometrial hyperplasia can be made by endometrial biopsy which is done in the office setting or through curettage of the uterine cavity to obtain endometrial tissue for histopathologic analysis. A workup for endometrial disease may be prompted by abnormal uterine bleeding, or the presence of atypical glandular cells on a pap smear.

Although there is no bona fide treatment for EH, most current guidelines recommend hormone therapies (including use of progestin, gonadotropin-releasing hormone (GnRH) or its analogues or their combination) or surgical treatment (Pic. 1). The selection criteria for treatment options are based on patient age, health, the presence of cytologic-atypia and fertility status (Pic. 2). EH without atypia responds well to progestins.

**Associated diseases**
- anemia
- polycystic ovary syndrome (PCOS) - endocrine and metabolic abnormalities that are left untreated in women with PCOS often develop into atypical endometrial hyperplasia and endometrial dysfunction-induced infertility
- endometrial carcinoma - endometrial hyperplasia is a significant risk factor for the development or even co-existence of endometrial cancer, so careful monitoring and treatment of women with this disorder is essential

**Complications**
- Endometrial hyperplasia has a high risk for malignant transformation and relapses.

**Risk factors**

Since EH is a precursor to cancer, all risk-factors of EC could be related to EH (Tab. 2).
- metabolic syndrome
- postmenopause
- during perimenopause
- insulin resistance
- type II diabetes
- polycystic ovary syndrome (PCOS)
- diabetes
- thyroid disease
- women over age 35
- never being pregnant
- obesity
- smoker

**Impact on fertility**

Many women are able to become pregnant with endometrial overgrowth, but it is major that you talk to your doctor regarding therapy options that thrifty to your fertility. In reality, studies have shown that about 30% of women who have endometrial overgrowth and choose for these types of treatments are able to have a live birth.

However, it is possible that women who have forward stages of this disease will find that their ability to become pregnant is complete stopped because of the treatments that are required to repair the issue. For this reason, it is relevant that you seek medical attention as soon as possible when you have been diagnosed with endometrial overgrowth.

Surgical methods (hysterectomy, hysteroscopic endometrial resection/ablation) lead to the removal or disruption of the endometrium and can cause infertility.
Prevention

- The primary role of progestin in postmenopausal estrogen therapy is endometrial protection to prevent hyperplasia.
- Eat a healthy diet.

Symptoms

- acne
- abnormal vaginal bleeding
- dryness of the vagina
- excessive growth of body hair
- menorrhagia
- hot flashes
- amenorrhea (absence of menstrual periods)
- mood swings
- pain during sexual intercourse
- rapid heart rate (tachycardia)
- severe fatigue
- tenderness of the vagina
- anovulatory periods (menstrual cycles without ovulation)

Therapies

Self therapy

Acupuncture

EH is from unbalance of hormones. Acupuncture try to treat unbalance of hormones and herbs may help causes of unbalance of hormones.

Conventional medicine

Pharmacotherapy

Progestin

Oral use of progestin, such as megestrol acetate (MA), and medroxyprogesterone acetate (MPA) is the most commonly used method with various regimens available for treatment of endometrial hyperplasia (EH). Nonetheless, the response rate is unsatisfactory, especially in atypical EH (approximately 70%). Progestin therapy may be continued or hysterectomy performed in cases of no response. Moreover, oral progestins are associated with poor compliance and systemic side effects that may limit overall efficacy. Different types of progestins and their doses in clinical use for the treatment of EH are shown in (Tab. 3 and 4).

Metformin

Metformin, insulin sensitizer, decreases insulin resistance by the inhibition of hepatic gluconeogenesis. Metformin not only lowers insulin levels and can also provide benefits by decreasing body weight, which diminishes the peripheral conversion of androgen. In addition, a low body index is related to a high resolution rate in EH patients with progestin treatment. Therefore, metformin may be proposed as an alternative agent for treatment of EH, especially for patients who have progestin resistance or other metabolic disorders.

Surgical therapy

Hysterectomy
Endometrial hyperplasia (EH), especially in the presence of atypia, has a strong tendency to the development of endometrial carcinoma. In this respect, hysterectomy is a preferred treatment for atypical EH. However, for young patient who desire to preserve their fertility or for patients not selected for surgery, conservative treatments using progestin are widely accepted as a treatment option.

### Assisted reproduction

Conservative treatment with high-dose progesterone for endometrial hyperplasia and well-differentiated early-stage adenocarcinoma followed by assisted reproductive technologies (IVF-ICSI) is an appropriate means for achieving pregnancy. If all efforts to conceive and carry a pregnancy to full-term fails, surrogacy may be considered.

### Find more about related issues

#### Diagnoses

**Obesity**  
A disease of excess body fat that can have a negative effect on health, leading to reduced life expectancy and other health problems.  
Learn more at: [www.fertilitypedia.org/therapy/diag/obesity](http://www.fertilitypedia.org/therapy/diag/obesity)

**Polycystic ovary syndrome**  
A condition in which a woman has an imbalance of female sex hormones. This may lead to changes in the menstrual cycle, cysts in the ovaries, trouble g  
Learn more at: [www.fertilitypedia.org/therapy/diag/polycystic-ovary-syndrome](http://www.fertilitypedia.org/therapy/diag/polycystic-ovary-syndrome)

**Endometriosis**  
A state in which pieces of the tissue alike to the lining of the uterus (endometrium) grow in other parts of the body.  
Learn more at: [www.fertilitypedia.org/therapy/diag/endometriosis](http://www.fertilitypedia.org/therapy/diag/endometriosis)

**Thyroid disorders**  
A medical condition impairing the function of the thyroid.  
Learn more at: [www.fertilitypedia.org/therapy/diag/thyroid-disorders](http://www.fertilitypedia.org/therapy/diag/thyroid-disorders)

**Endometrial cancer**  
Cancer that arises from the endometrium, the lining of the uterus.  
Learn more at: [www.fertilitypedia.org/therapy/diag/endometrial-cancer](http://www.fertilitypedia.org/therapy/diag/endometrial-cancer)

**Amenorrhoea**  
The absence of a menstrual period in women of reproductive age.  
Learn more at: [www.fertilitypedia.org/therapy/diag/amenorrhoea](http://www.fertilitypedia.org/therapy/diag/amenorrhoea)

**Oligomenorrhea**  
Light or infrequent menstrual flow at intervals of 39 days to 6 months or 5–7 cycles in a year.  
Learn more at: [www.fertilitypedia.org/therapy/diag/oligomenorrhea](http://www.fertilitypedia.org/therapy/diag/oligomenorrhea)

#### Organs

**Uterus**  
The uterus is the largest and major organ of the female reproductive tract that is the site of fetal growth and is hormonally responsive  
Learn more at: [www.fertilitypedia.org/edu/organs/uterus](http://www.fertilitypedia.org/edu/organs/uterus)

#### Reproductive cells
Endometrium
The innermost layer of uterus forming the uterine lumen where the implantation of an oocyte happens.
Learn more at: www.fertilipedia.org/edu/reproductive-cells/endometrium

## Biological control

### Estrogen
The primary female sex hormone responsible for the development and regulation of the female reproductive system and secondary sex characteristics.
Learn more at: www.fertilipedia.org/edu/biological-control/estrogen

### Progesterone
Steroid hormone, secreted by the ovaries, whose function is to prepare the uterus for the implantation of a fertilized ovum and to maintain pregnancy.
Learn more at: www.fertilipedia.org/edu/biological-control/progesterone

## Reproductive functions

### Implantation
The very early stage of pregnancy at which the embryo adheres to the wall of the uterus.
Learn more at: www.fertilipedia.org/edu/reproductive-functions/implantation

## Risk factors

### Anemia
A decrease in the amount of red blood cells or hemoglobin in the blood.
Learn more at: www.fertilipedia.org/therapy/rr/anemia

### Diabetes mellitus
A condition in which the body either does not produce enough, or does not properly respond to insulin, a hormone produced in the pancreas.
Learn more at: www.fertilipedia.org/therapy/rr/diabetes-mellitus

### High level of estrogen
A medical condition characterized by an excessive amount of estrogenic activity in the body.
Learn more at: www.fertilipedia.org/therapy/rr/high-level-of-estrogen

### Obesity
A medical condition of excess body fat that can have a negative effect on health, leading to reduced life expectancy and other health problems.
Learn more at: www.fertilipedia.org/therapy/rr/obesity

### Smoking
Long lasting inhalation of the smoke of burning tobacco.
Learn more at: www.fertilipedia.org/therapy/rr/smoking-1

## Symptoms

### Absence of menstrual periods
The absence of a menstrual period in a woman of reproductive age.
Learn more at: www.fertilipedia.org/edu/symptoms/absence-of-menstrual-periods-1

### Absence of ovulation
An anovulatory cycle is a menstrual cycle during which the ovaries do not release an oocyte.
Learn more at: www.fertilipedia.org/edu/symptoms/absence-of-ovulation-1
Acne
A long-term skin condition characterized by areas of blackheads, whiteheads, pimples, greasy skin, and possibly scarring.
Learn more at: www.fertilitypedia.org/edu/symptoms/acne

Excessive facial and body hair growth in women
The excessive hairiness on women in those parts of the body where terminal hair normally is absent or minimal, such as a beard or chest hair.
Learn more at: www.fertilitypedia.org/edu/symptoms/excessive-facial-and-body-hair-growth-in-women-1

Fatigue
A subjective feeling of tiredness which is distinct from weakness, which has a gradual onset.
Learn more at: www.fertilitypedia.org/edu/symptoms/fatigue

Heavy or prolonged bleeding in menstrual period
Abnormally heavy or prolonged bleeding in menstrual periods.
Learn more at: www.fertilitypedia.org/edu/symptoms/heavy-or-prolonged-bleeding-in-menstrual-period-1

Infrequent menstruation
The medical term for infrequent, often light menstrual periods (intervals exceeding 35 days).
Learn more at: www.fertilitypedia.org/edu/symptoms/infrequent-menstruation-1

Painful sexual intercourse
The painful feelings during sexual intercourse.
Learn more at: www.fertilitypedia.org/edu/symptoms/painful-sexual-intercourse

Vaginal bleeding
Irregular intermenstrual bleeding including postcoital bleeding.
Learn more at: www.fertilitypedia.org/edu/symptoms/vaginal-bleeding

Vaginal dryness
Decreased or missing lubrication of vagina.
Learn more at: www.fertilitypedia.org/edu/symptoms/vaginal-dryness

Therapies

Acupuncture
A form of alternative medicine and a key component of traditional Chinese medicine involving thin needles inserted into the body at acupuncture points
Learn more at: www.fertilitypedia.org/edu/therapies/acupuncture

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

Hysterectomy
Surgical removal of the uterus.
Learn more at: www.fertilitypedia.org/edu/therapies/hysterectomy

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi
Pharmacotherapy of endometrial hyperplasia
Drugs, which are used as a treatment option of endometrial hyperplasia.
Learn more at: www.fertilitypedia.edu/therapies/pharmacotherapy-of-endometrial-hyperplasia

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.edu/therapies/standard-ivf

Surrogacy
The embryo is gestated in a third party’s (surrogate) uterus.
Learn more at: www.fertilitypedia.edu/therapies/surrogacy

Tab

Common drugs for treatment of endometrial hyperplasia

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Origin and formula</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestin therapy</td>
<td>Synthetic progesterone (17β-estradiol)</td>
<td>Oral, intramuscular</td>
</tr>
<tr>
<td></td>
<td>Mifepristone</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Medroxyprogesterone acetate</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Leuprolide acetate</td>
<td>Intramuscular</td>
</tr>
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<td></td>
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<td>Intramuscular</td>
</tr>
<tr>
<td></td>
<td>Luteinising hormone</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td>Intrauterine device</td>
<td>Oral</td>
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<th>Therapy type</th>
<th>Common name</th>
<th>Common drug for endometrial hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestins</td>
<td>Progesterone, Danazol</td>
<td>200-400 mg PO</td>
</tr>
<tr>
<td>Synthetic progestin</td>
<td>Dronedarone (Carnitine)</td>
<td>10-20 mg PO</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>Mifepristone</td>
<td>15 mg PO</td>
</tr>
</tbody>
</table>

Endometrial hyperplasia
Low magnification micrograph of simple endometrial hyperplasia without nuclear atypia.

Pic. 2: The investigations and management schemes for endometrial hyperplasia

Investigation:
- Vaginal ultrasound
- Endometrial biopsy
- Dilation and curettage (D&C)
- Hysteroscopy

Management:
- Simple hyperplasia
  - Low dose progestin
  - Complex hyperplasia
  - Low dose progestin
  - High dose progestin
  - Atypical hyperplasia
  - Low dose progestin
  - High dose progestin
  - Hysterectomy
  - Progesterone
  - Hormone replacement therapy
  - Ovarian suppression
  - GnRH agonist
  - LNG-impregnated intrauterine device
  - Oral contraceptive
  - Acupuncture
  - Regular vaginal bleeding
  - Aromatase inhibitors
  - Anti-estrogen therapy
  - GnRH antagonist
  - Gonadotropin-releasing hormone agonist

Endometrial hyperplasia
Low magnification micrograph of simple endometrial hyperplasia without nuclear atypia.
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