

# **ENDOMETRIAL HYPERPLASIA**

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## **\*Introduction..**

-**The** chance of developing endometrial hyperplasia (EH) may be increased during menarche and perimenopause. These periods are characterized by anovulatory cycles; therefore, relatively unopposed endogenous estrogen can result in development of EH.

-**Indeed**, any condition with an increase in unopposed estrogen can result in EH or endometrial carcinoma. Obesity, polycystic ovarian syndrome with chronic anovulation, estrogen-producing tumors, ovarian stromal tumors, and estrogen-only replacement therapy are all associated with increased risk of EH and/or endometrial carcinoma.

**NB:** estrogenic effect on endometrium... **cells** (columnar)... **glands** (increase number & become elongated & dilated) ...**stroma** (increase cellularity)...**blood vessels** (increase vascularity).

- **The** prevalence of EH is generally estimated to be 1 case per 1000 women. The prevalence rate of simple EH in asymptomatic menopausal women is 4% and ranges from 4-30% in symptomatic menopausal women (having abnormal uterine bleeding).

## **\*Definition...**

-A spectrum of alteration of endometrial glands & stroma ranging from normal endometrium to endometrial carcinoma.

- Endometrial hyperplasia (EH) is a condition that occurs when the lining of the uterus (endometrium) grows too much. It is a benign (not cancer) condition.

- A condition where the endometrium (lining of the uterus) becomes overgrown, usually related to too much estrogen, or an imbalance between estrogen and progesterone.

- This disease is a frequent precursor to cases of endometrial carcinoma of the uterus.

## **\*Etiology...**

# EH is commonly associated with:

\***Anovulatory menstrual cycles**:- Immediately after the menarche , In the latter years preceding the menopause.

\***Hormone replacement therapy & Also patient with tamoxifen treatment.** (Tamoxifen, a synthetic anti-estrogen that paradoxically acts as a partial estrogen agonist on the endometrium , is associated with an increased frequency of proliferative endometrial lesions, including hyperplasias, neoplasms , and polyps).

\***Polycystic Sclerotic Ovaries**

\***Obesity**:- Peripheral conversion of androstenedione to oestrone; especially in postmenopausal women.

\***Oestrogen producing tumors** e.g. granulosa-theca ovarian tumors - but these are rare.

## **So, Ask About.... Who Is at Risk?**

#**EH** is more likely to occur in certain women. Those most at risk are women who:

- \*Are in the years around menopause.
- \*Skip menstrual periods or have no periods at all.
- \*Are overweight.
- \***H**ave diabetes.. Hyperinsulinemia may have a direct mitogenic effect on the endometrium.
- \***H**ave polycystic ovary syndrome.
- \***T**ake estrogen without progesterone to replace the estrogen their body is no longer making and to relieve symptoms of menopause.

### **\*Pathology...**

#### **# Macroscopic Picture...**

- Uterus symmetrically enlarged, myohyperplasia, thick endometrium may be with polpi & hemorrhage.
- Ovarian enlarged showing POC or follicular cyst.

#### **# Microscopic Picture...**

### **Old Classification...**

#### **1- Simple glandular hyperplasia..**

Just increase number of endometrial cells & glands.

#### **2- Cystic glandular hyperplasia = Swiss cheese hyperplasia..**

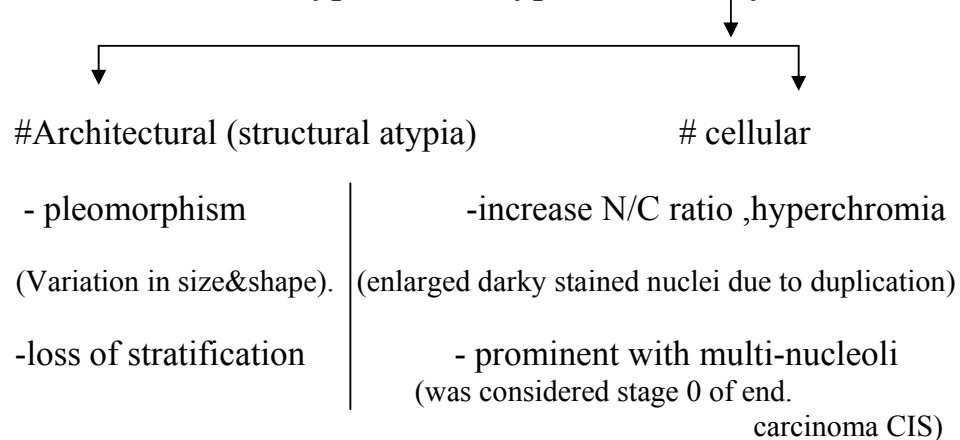
Commonest type of end. Hyper. characterized by:

- dilated glands lined by cuboidal or tall columnar epith.
- No cellular atypia... (Atypia is defined as stratified cells with loss of polarity, loss of normal relation between each cell & the neighboring one & surrounding tissue) and increased nuclear/cytoplasmic ratio).
- No or moderate crowding...

### 3- Adenomatous end. hyperplasia..

- Crowding of glands & acini show multilayers (stratification) with budding into lumen & stroma.
- No cellular atypia..

### 4- Adenomatous end. Hyper. with atypia which may be:



## Recent classification...

### International Society of Gyn. Pathology & WHO

#### 1-Simple hyperplasia...(cystic glandular hyperplasia)

- hyperplasia of both the epithelial cells lining the glands and the stromal cells. The glands may be greatly dilated and visible to the naked eye on section, giving rise to the description of Swiss cheese appearance.

#### 2-Complex hyperplasia..(adenomatous hyperplasia)

- active proliferation of the glandular epithelium but not of the stroma. The endometrium shows glands crowded together with little

intervening stroma. About 20% progress to endometrial adenocarcinoma.

<b>Simple</b>	Increase in the glandular and stromal components with slight architectural abnormalities
<b>Complex</b>	Crowded glands with little intervening stroma Back to back glands and papillary intraluminal infoldings

3- **Atypical hyperplasia..** (severed hyper = adenomatous hyperplasia. with atypia) Complex pattern + cellular atypia = CIS.

**NB:** In all types lack of stromal invasion differentiate them from end. carcinoma G1

### **\*Complications...**

\*Risk of progression to end carcinoma estimated as:

Recent names	Risk
- simple hyper .....	1% after 16y
- complex hyper.....	5% after 8y
- atypical hyper.....	20% after 4y

### **\*Diagnosis...**

\* Endometrial hyperplasia is usually suspected on clinical grounds.

\*Diagnosis is confirmed by D+C and endometrial biopsy.

\*The most common symptom of hyperplasia is abnormal vaginal bleeding.

\*Most women present with prolonged, heavy or intermenstrual bleeding and are over age 40 or postmenopausal.

### **\*\*History**

- **Premenopausal** women with EH usually present with heavy or prolonged menstrual bleeding, intermenstrual bleeding, or prolonged episodes of amenorrhea.

- **Postmenopausal** women with EH most commonly present with vaginal bleeding or spotting.

- **During perimenopause**, transition bleeding patterns can be irregular. The normal pattern of bleeding in the transition to menopause should be further and further apart, and lighter and lighter. Flow should be no closer together than 21 days and should last no longer than 7 days, with no spotting, bleeding, or dirty discharge at all. Any deviation from this pattern requires evaluation.

### **\*\*Physical**

-The evaluation of abnormal vaginal bleeding requires a thorough physical examination of the vulva, vagina, and cervix, as well as an endometrial evaluation. In most patients with EH, there are no gross findings on physical examination. The uterus can be normally sized or slightly enlarged.

-The patient may show evidence of other conditions associated with endogenous estrogen such as obesity (conversion of androstenedione to estrogens in fat), stigmata of androgen excess observed in polycystic ovarian syndrome as hirsutism, enlarged clitoris, or acne. An adnexal mass may be present in patients with estrogen-producing tumors.

## **\*\*Workup**

### **Imaging studies**

-Transvaginal ultrasound: This has been used to provide a measure of endometrial thickness. In postmenopausal women, a transvaginal pelvic ultrasound can effectively exclude hyperplasia or cancer if the endometrial stripe measures  $<5$  mm, however many women will have a thicker endometrial stripe and require biopsy.

### **Other tests**

- Saline infusion sonohysterography: This can be used as an adjunct to the evaluation of bleeding and is very helpful in identifying intrauterine lesions such as polyps or submucous leiomyomas.

### **Procedures**

#### **- Endometrial biopsy**

The office endometrial biopsy has replaced the fractional dilatation and curettage (D&C) as the usual first diagnostic step in evaluation of abnormal uterine bleeding.

For women with severe cervical stenosis, or those unable to tolerate office-based endometrial sampling, D&C under anesthesia may be required.

#### **- Hysteroscopy**

This diagnostic procedure has been used to obtain directed biopsies of abnormal-appearing areas of the endometrium. In the operating room setting, a fractional D&C usually follows a hysteroscopy (by convention).

**NB:** EH may be a symptomatic accidentally discovered during endometrial sampling for screening for endometrial care.

## **WHO NEEDS AN ENDOMETRIAL BIOPSY?**

-Indications for Endometrial Biopsy

### **1) Postmenopausal Bleeding:**

-Any woman with postmenopausal bleeding who is not on hormone replacement therapy (HRT) requires endometrial sampling. About 7% of such cases are caused by malignancy.<sup>12</sup> Thus, postmenopausal bleeding should be considered to be from endometrial cancer until proven otherwise.

- Most women on cyclic combined HRT experience regular withdrawal bleeding. Patients with irregular bleeding, not associated with progesterone withdrawal, should be considered to have an abnormal pattern of bleeding and should have endometrial sampling.<sup>6,8</sup>

- Women on continuous combined HRT, the endometrium often becomes atrophic, and these women become amenorrheic. Seventy-five percent of these women develop amenorrhea after six months.<sup>13</sup> If bleeding occurs beyond six months, this should be considered abnormal, and endometrial sampling should be considered.<sup>6</sup>

### **2) Perimenopausal Bleeding:**

- During the perimenopausal years, waxing and waning ovarian function produces changes in the menstrual cycle. Women often experience cycles that vary in length as well as amount and duration of flow.

- Perimenopausal women with abnormal bleeding are at increased risk of endometrial cancer secondary to their age and anovulatory cycles. Thus, all women with abnormal uterine bleeding in the perimenopausal period require endometrial sampling.<sup>9,14</sup> The most suspicious patterns are persistently increased menstrual flow, decreased menstrual interval, and intermenstrual bleeding.<sup>14</sup>

### **3) Premenopausal Bleeding:**

-Adolescents generally do not require sampling because their abnormal bleeding is often due to anovulation secondary to an immature hypothalamic-pituitary-ovarian axis. Less commonly, an underlying inherited coagulopathy may be the cause.

- However, after the adolescent period, endometrial cancer should be considered in the differential diagnosis of abnormal bleeding because up to 10% of women with endometrial cancer are diagnosed before the age of 45.<sup>10</sup>

#### **4) Abnormal Pap Smear Cytology:**

- In postmenopausal women, the presence of any endometrial cells on Pap smear is an indication for endometrial sampling.<sup>6,9</sup> In other women, the presence of atypical endometrial cells also warrants an endometrial biopsy. Patients with malignant endometrial cells on Pap smear are at significant risk of having endometrial cancer, often a high-grade malignancy.<sup>15</sup>

#### **5) Follow-up:**

- Women who have been treated for endometrial hyperplasia with hormonal therapy require a follow-up endometrial biopsy in 3 to 6 months to ensure the hyperplasia has regressed.

#### **6) Role for Screening with Endometrial Biopsy:**

-There is no role for screening women who do not present with abnormal bleeding. Asymptomatic women are at low risk for endometrial cancer,<sup>16</sup> and the accuracy of endometrial biopsy is poor for well-differentiated, low-volume, minimally invasive tumors, which makes endometrial sampling a poor screening test.<sup>17</sup>

### **CONCLUSION:**

- Outpatient endometrial biopsy has modest accuracy in diagnosing endometrial hyperplasia. Therefore, additional endometrial assessment should be undertaken, especially if symptoms persist or intrauterine structural abnormalities are suspected.

### **\*Treatment...**

-In most cases, endometrial hyperplasia can be treated with medication that is a form of the hormone progesterone. If the problem persists, more treatment may be used. Most types of hyperplasia respond well to hormonal therapy.

## \*\*Prophylactic management...

- Avoid prolonged anovulation.
- Screening for high risk group.

## \*\* Active management..

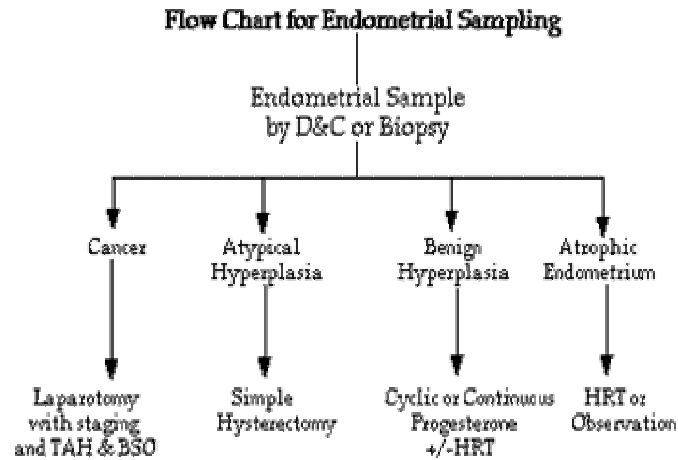
-Two important factors must be considered:

- 1- Age of patient & her need for pregnancy
- 2- Histological grad of hyperplasia .

\* Cystic hyperplasia in a young woman may be treated with a cyclical progestogen - such as norethisterone for 10 days each month. Hysterectomy may be indicated in an older woman.

\* Management of adenomatous hyperplasia must always bear in mind the likelihood of progression to malignancy. Cyclic progestogens or hysterectomy are the two alternatives. The latter is advised in older patients, those with significant cellular atypia, and those with other factors associated with increased risk of endometrial carcinoma e.g. obesity, nulliparity.

Age	Simple H.	Complex H.	Atypical H.
post-pubescence	-Usu. Regress spont. No clo → none  Clo = DUB → Progestins	Same treat	-Very rare  -Progestins or  Induction of ovulation
CBP (usu. 2ry to anovulation)	Pt. want preg → induct  Pt. don't want preg: → No C/e → no tret. → DUB → progest	Want preg → indu  Don't want preg: → progestins	Rare  Treat as complex
Pre or Post menopausal	Progestins	-Progestins -Hysterectomy	-Hysterectomy -Progestins if risk



\*Any patient treated conservatively (progest or ovulation induction) must be followed up 3 months latter to document regression of hyperplasia. (if progressing → hysterectomy is considered).

**Table 1. Follow-up of Patients with Hyperplasia\***

Degree of Hyperplasia	Number of Patients	Regressed	Persisted	Progressed to Carcinoma
Simple	92	74 (80%)	17 (19%)	1 (1%)
Complex	29	23 (80%)	5 (17%)	1 (3%)
Simple atypical	13	9 (69%)	3 (23%)	1 (8%)
Complex atypical	25	20 (57%)	5 (14%)	10 (29%)

\*(Kurman et al, 1985)

### \*Progesterone administration...

- Medroxyprogesterone acetate (Provera): 10-20 mg for 12-14 days per month.
- Norethindrone acetate (Aygestin): 5 mg for 12-14 days per month.
- Micronized progesterone (Prometrium): 200 mg for 12-14 days per month . Common side effects of Prometrium Capsules are breast tenderness, dizziness, abdominal bloating, and vaginal discharge.
- Progesterone-containing intrauterine device.....Progestasert (Mirena) for 1-5 years.

### \*High-dose progestogens...

- Medroxyprogesterone acetate (Provera): 40-100 mg per day for at least 3 months.
- Megestrol acetate (Megace): 40 mg per day

\*Anti-estrogen as danazol & LH-RH analogue can be used in place of progesterone (more expensive).

**\*NB:** Endometrial cancer and hyperplasia have long been associated with diabetes. Hyperinsulinemia may have a direct mitogenic effect on the endometrium and may inhibit the effect of progestogen therapy.

**\*\*\*This case report describes the treatment of a patient with atypical endometrial hyperplasia with an insulin-sensitizing agent.**

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\*A 37-year-old patient presented after failed treatment of endometrial hyperplasia with progestogen therapy. One month after initiating metformin therapy the patient's endometrial

biopsy demonstrated proliferative endometrium. This patient's atypical endometrial hyperplasia regressed after the initiation of treatment with an insulin-sensitizing agent. This relatively new class of drugs may provide an adjunct to the therapy of endometrial hyperplasia.

## **\*\*Endometrial Ablation**

\* Endometrial ablation (EA)——→removing the lining of a woman's uterus. EA is an alternative to both long term drug therapy & hysterectomy for women who have excessive menstrual or uterine bleeding.

\* Ablation procedures can prevent the need for 80 -90 % of currently performed hysterectomies.

**NB:** about 1/3 of hysterectomies procedures were done for menorrhagia & in About 1/2 of these cases uterus was histologically normal.

\* In contrast to a hysterectomy an ablation procedure is performed either in gynecological office or as an outpatient surgery, with patient's returning home the same day, and without the need for an abdominal or vaginal incision.

## **Types...**

\* The original ablation procedure involved the use of an argon laser, but was time-consuming and expensive to perform. In 1990, Roller Barrell ablation was introduced, which was easier to perform and required less complex and less costly surgical equipment. However, an experienced gynecologic endoscopic surgeon is required.

**These are called: "First Generation EA techniques"**

**\*Now..."Second Generation EA techniques", "SEAT" ,** have been developed and are available in the United States.

## **\*\*Benefits of SEAT..**

- Easier to perform, Easier to learn by physicians.
- Have very high success rates.
- Safer than first generation devices.
- Can be performed in doctor's office , taking only 15 minutes.
- Not require major anesthesia.

**\*\*These second generation devices use various methods for destroying the endometrial cavity, including:**

1-Radio frequency...(heating endometrium to cytotoxic level "66<sup>0</sup>c" by radiofrequency .electromagnetic thermal energy delivered by probe placed inside uterine cavity ,slowly rotated 360<sup>0</sup> over 20 minutes " done without hysteroscopy").

2- Lasers...(introduced by Goldrath 1981 ,laser can be delivered along narrow , 0.6mm, diameter flexible fiber transmitted through liquid media) .

3-Electrocautary...(introduced by Newwirth 1983 ,by electrocautary of the uterine cavity by systematically shaving the endometrium as far as the isthmus using the cutting loop of the resecting hystroscope.

## **\*\* Procedure**

\* Time of the EA procedure... most first & second generation EA devices can be performed immediately following a menstrual period. The menstrual cycle may need to be modified before the ablation procedure..(can be done by suppression of ovarian hormones and the uterine lining using a GnRH analogue...expensive). One of the second generation EA devices does not require any pretreatment of a woman's endometrium.

\* Recovery... - Most women have a brownish to bloody vaginal discharge for up to 6 weeks following EA. (Avoid strenuous activities or exercise for two weeks, to minimize excess bleeding).

- In contrast to a hysterectomy, which may require up to 8 weeks for recovery, most women who have EA are able to return to most normal activities within 2-3 days.

- EA may prevent future pregnancy, but it should not be considered a sterilization technique, and other method(s) of contraception should be used by women who wish to avoid pregnancy.

### **\*\*Risks..**

\* Most potential complications of EA involve use of the 1<sup>ST</sup> Generation devices...These include: risks of anesthesia, uterine perforation, and absorption of large volumes of fluid used during the ablation procedure (fluid overload). Patient deaths have been reported from this latter complication.

\* The SEATs have the advantage of not using high volumes of, or dangerous fluids, requiring less anesthesia, requiring less time to complete, and many cases can be performed in office rather than a hospital.

### **Finally ...**

Women with endometrial hyperplasia can be treated. In most cases, women at risk can take steps to protect against endometrial hyperplasia.

تم عرضها



