Endometrial Hyperplasia &Endometrial Intraepithelial Neoplasia

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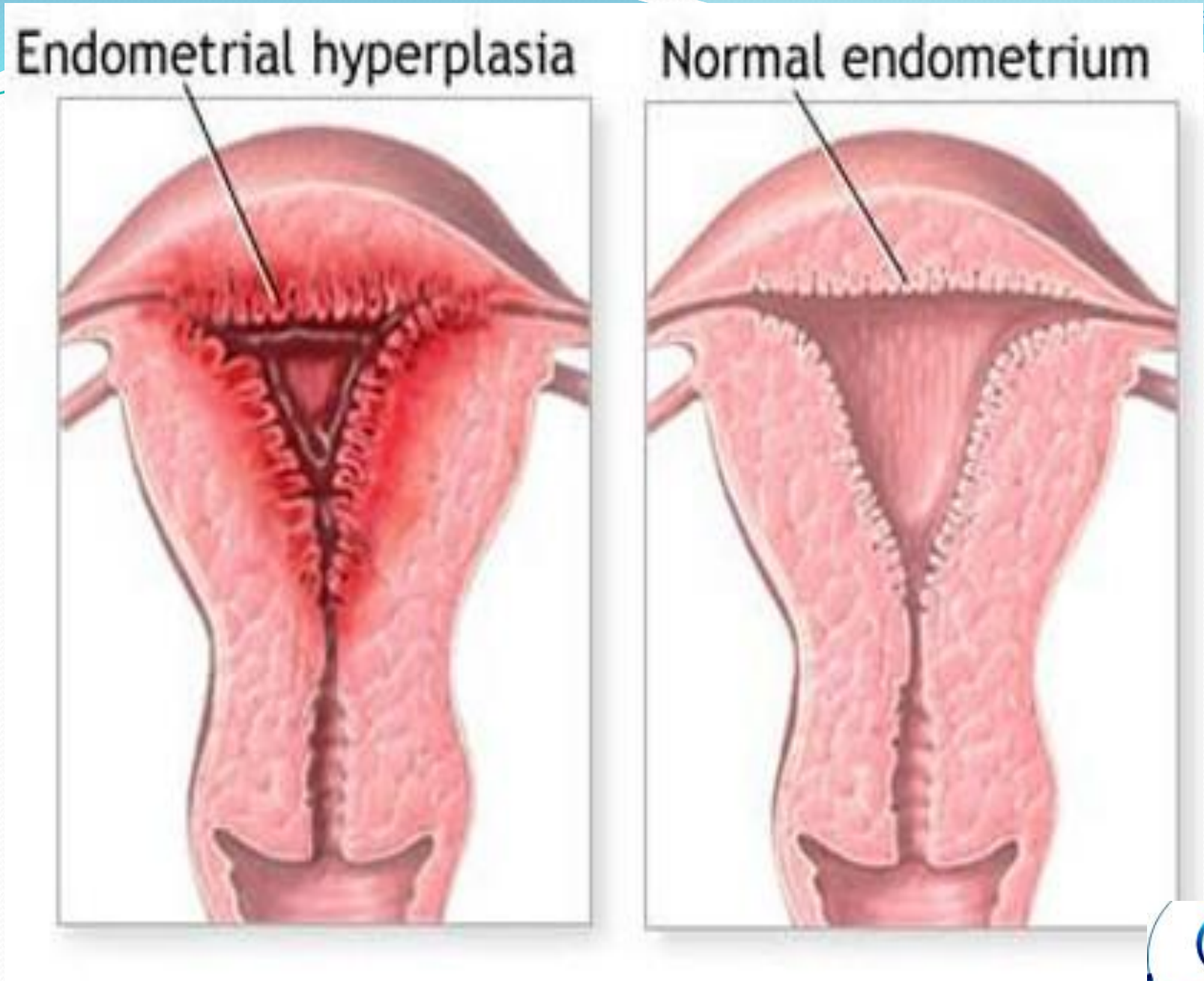
Endometrial Hyperplasia

- It is noninvasive proliferation of the endometrium that results in a morphologic pattern of glands with irregular shapes and varying size
- Actual incidence is still unknown but it is estimated to be seen in 1.5% of patients with abnormal uterine bleeding
- Clinical significance is the underlying genital malignancy which is around 5%



Risk Factors

- Unopposed estrogen is the most well known risk factor for EH
- Estrogen has both mutagenic and carcinogenic effects on endometrial glands and stroma
- Be alert for EH in the following conditions:
- 1-Abnormal uterine bleeding in women > 40 years old
- 2-Abnormal uterine bleeding with :PCO, chronic anovulation, Obesity, Tamoxifen use
- 3-All abnormal bleeding refractory to treatment
- 4-Patients receiving unopposed estrogen therapy
- 5-Atypical glandular cells on cervical smear
- 6-Presence of endometrial cells in cervical smears of >40-year-old patients
- 7-Patients with hereditary nonpolyposis colorectal cancer

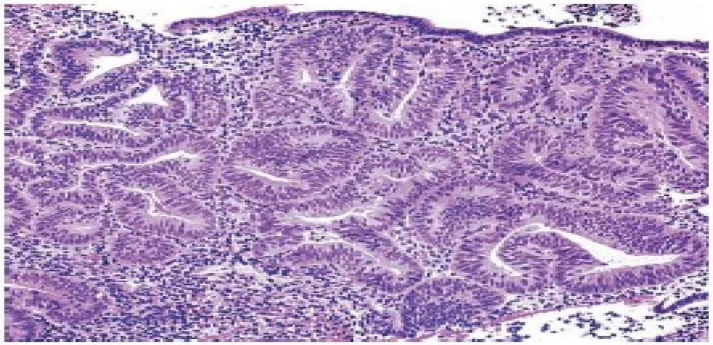
Classification& Behavior

- WHO94 classification
- Based on presence or absence of atypical cells and the structural pattern

Type	Description	Risk of Progression to Endometrial Cancer
Simple	Dilated glands that may contain some outpouching and abundant endometrial stroma	~ 1%
Complex	Glands are crowded with very little endometrial stroma, and a very complex gland pattern and outpouching formations	~ 3%-5%
Simple with atypia	Is the same as above, but also contains cytologic atypia. This refers to hyperchromatic, enlarged epithelial cells with an increased nuclear to cytoplasmic ratio.	~ 8%-10%
Complex with atypia		~ 25%-30%

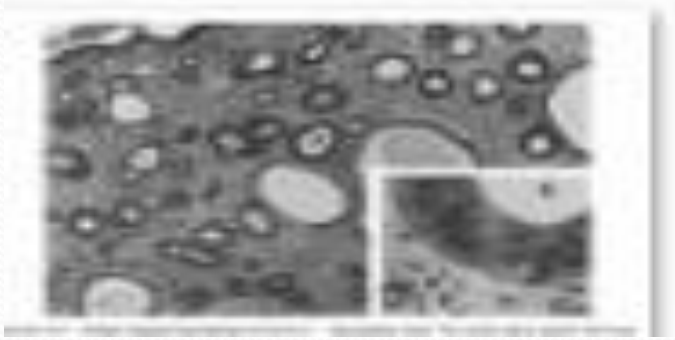
Non atypical simple and complex hyperplasia

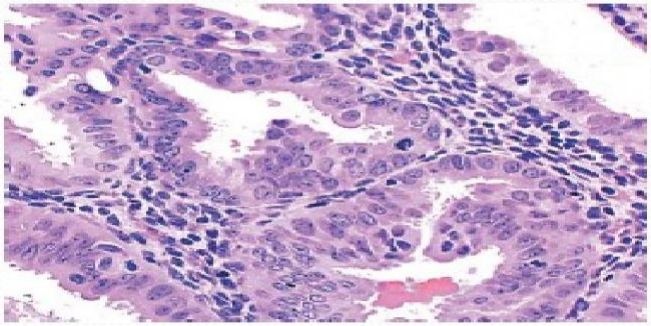
- **Simple Hyperplasia**
- The glandular cell nuclei are oval and pseudostratified with uniform outlines lacking cytological atypia
- Nucleoli are indistinct
- Both glandular and stromal cells are cytologically similar to those of proliferative phase endometrium



- **Complex Hyperplasia**
- Glands are closely packed, lacking the abundant stroma seen in simple hyperplasia
- There is no atypia

Atypical simple and complex Hyperplasia





- **Simple Atypical EH**
- Several glands are cystic and there is moderate amount of intervening stroma
- Nuclei show atypia…they are round, vesicular and stratified

- **Complex Atypical EH**
- Glands are haphazardly distributed losing orientation to the underlying basement membrane
- Nuclei are rounded and vesicular with prominent nucleoli

Endometrial Intraepithelial Neoplasia (EIN)

- Because of limited number of studies there is an on-going debate about diagnosis, classification and treatment
- In 2002 The Endometrial Collaborative Group developed a new classification system called EIN

EIN Terminology	Topography	Functional category	Treatment
EH	Focal	E2 effect	Hormonal
EIN	Focal, diffuse	precancer	Hormonal Surgical
Cancer	Focal, diffuse	Cancer	Surgical

EIN Criteria

- D-score (morphometric score)
- It is a measure of clonality and precancerogenisity
- Vary between -4 and +4
- D-Score is evaluated by using 3 main pathological criteria:
- 1-VPS..Volume percentage stroma should be <55%
- 2-OSD.. Outer surface diameter measuring the branching of glands
- 3-SDSNA.. Standard deviation of shorter nuclear axis– a scale for nuclear variation
- If D-score is <1 there is high propensity for progression to cancer
- If D-Score is >1 no progression was seen in 22 years of follow up

- Sensitivity and negative predictive value for D-Score is 100%
- Sensitivity for WHO classification is 89% and negative predictive value is 94%

EIN System VZ WHO94 classification

- Sensitivity and negative predictive value for D-Score is 100%
- Sensitivity for WHO classification is 89% and negative predictive value is 94%
- D-Score enables physician to make more standardized diagnosis and therefore more algorithmic treatments
- NB. Because we do not know the cost-effectiveness and absence of routine use the WHO system is the accepted one so far.

Diagnosis

- The gold standard for diagnosis is endometrial biopsy
- Optimal time for biopsy is just after withdrawal bleeding since exogenous progestin may affect the pathological evaluation
- Office endometrial biopsy using pipelle and vabra techniques was shown to be cost-effective with prediction of carcinoma in 97-99% and EH in 66.7-82.3%
- Cases with insufficient material or in cases where clinical suspicious continues, classical dilatation and curettage is indicated
- Office hysteroscopy have 48-71% positive predictive value and 92-95% negative predictive value for EH
- NB. There is a controversial risk of peritoneal dissemination during office hysteroscopy in cases with carcinoma therefore the initial diagnosis should be office biopsy and if hysteroscopy used it should be used with low flow pressure

Treatment of EH

- **EH cases should be treated by gynecological oncologist due to the risk of concomitant endometrial or ovarian carcinoma**
- **An experienced pathologist has a crucial role in treatment**

- **Treatment depends on :**
- *Type and related malignant potential of EH
- *patient age and desire for fertility
- *medical condition of the patient
- *Presence of other gynecological conditions e.g fibroid, ovarian lesion…

- **Type of treatment:**
- 1- Medical treatment
- 2- surgical treatment

Medical Treatment of EH

- Progestagen is the most effective and most cost-effective treatment option
- Response to progestogen:
- Atypical hyperplasia treated with low doses showed 80% response rate, persistent rate 6%, recurrent rate 14% and 0% cancer progression
- Typical hyperplasia treated with high doses showed variable response with 87-100% response rate (Ferenzy; Gelfand, Am.J.Obstet.Gynecol,1989)
- Type of progestin: there is no significant difference with respect to type of progestin used
- There is no data showing whether cyclic or continuous treatment is better
- Endometrial biopsy is required every 3-6 months

Medical Treatment of EH (cont.)

- **1-Progestin**

-Low dose (12-14days/month)

*Medroxyprogesterone acetate (porvera) 10-20mg/day

*Norethindrone acetate 5mg/day

*Micronized progesterone (oral progestan, vaginal cyclogist)200mg/day

*Mgaestrol acetate (Megace)20-40mg/day

-High dose (21days/month)

*Medroxyprogesterone acetate 40-100mg/day

*Micronized progesterone 300-400mg/day

*Megace 80-160mg/day

2-Oral contraceptives

3-Ovulation induction

4-Levonorgestrel containing intrauterine devices (Mirena)

5-Danazol 400mg/day (3 months)

6-GnRH analogues e.g Triptorelin 3.75 mg for 3-6 months

7-Aromatase Inhibitors

8-Mifepristone (RU486)

Surgical Treatment For EH

- Indications:
- *Failure of Medical treatment
- *patient above the age of 40 years not desiring conception with atypical hyperplasia
- *Failure of follow up of patient

Methods

1- Endometrial Curettage

2-Endometrial Ablation and Resection…young <40 years patients without atypical hyperplasia

3-Hysterectomy. Considered in atypical hyperplasia and in patients above the age of 40 years

Thank You

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