Early detection of Endometrial Cancer

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Epidemiology

According to ACS 2015:

- Endometrial cancer: **most** common **female** pelvic genital cancer .
- The ***life time risk*** of developing it is 2.4% (In USA).
  (No recent available statistics in EGYPT)
- Age: - Peak incidence in the 6^{th} & 7^{th} decade of life
  - Only 2-5% occur before 40 years.
- Higher survival rate due to early diagnosis (75% diagnosed in Stage I).
- Estrogen has been implicated as a causative factor.

Epidemiology

- Endometrial hyperplasia is the precursor of endometrial cancer which is the most common gynecological malignancy in the Western world .

- The incidence of endometrial hyperplasia is estimated to be at least three times higher than endometrial cancer.

(GTG 67: feb 2016))

Risk factors

1- *increased body mass index* (BMI) ; with excessive peripheral conversion of androgens in adipose tissue to estrogen;

2- *Anovulation* associated with the peri-menopause or polycystic ovary syndrome (PCOS)

3- *Estrogen-secreting ovarian tumors*, e.g. granulosa cell tumors (with up to 40% prevalence of endometrial hyperplasia);

4- *drug-induced endometrial stimulation*, e.g. the use of systemic ERT or long-term tamoxifen

Risk Factors

OLD AUNT:

Obesity

Late menopause

Diabetes mellitus

Another cancer; ovary, endometrium, colon

Unopposed estrogen

Tamoxifen prolonged use

Early detection/screening (NCI-USA)

Transvaginal Ultrasound

- Benefits: There is no evidence that screening by ultrasonography reduces mortality from endometrial cancer. Most cases of endometrial cancer (85%) are diagnosed at low stage because of symptoms, and survival rates are high.

Early detection/screening (NCI-USA)

Transvaginal Ultrasound

- Harms: Based on solid evidence, screening asymptomatic women will result in unnecessary additional biopsies because of false-positive test results. Risks associated with false-positive tests include anxiety and complications from biopsies.

Early detection/screening (NCI-USA)

Endometrial Sampling (Biopsy)

- **Benefits:** There is inadequate evidence that screening by endometrial sampling (i.e., biopsy) reduces mortality from endometrial cancer. Most cases of endometrial cancer (85%) are diagnosed at low stage because of symptoms, and survival rates are high.

Early detection/screening (NCI-USA)

Endometrial Sampling (Biopsy)

- Harms: Based on solid evidence, endometrial biopsy may result in discomfort, bleeding, infection, and rarely, uterine perforation.

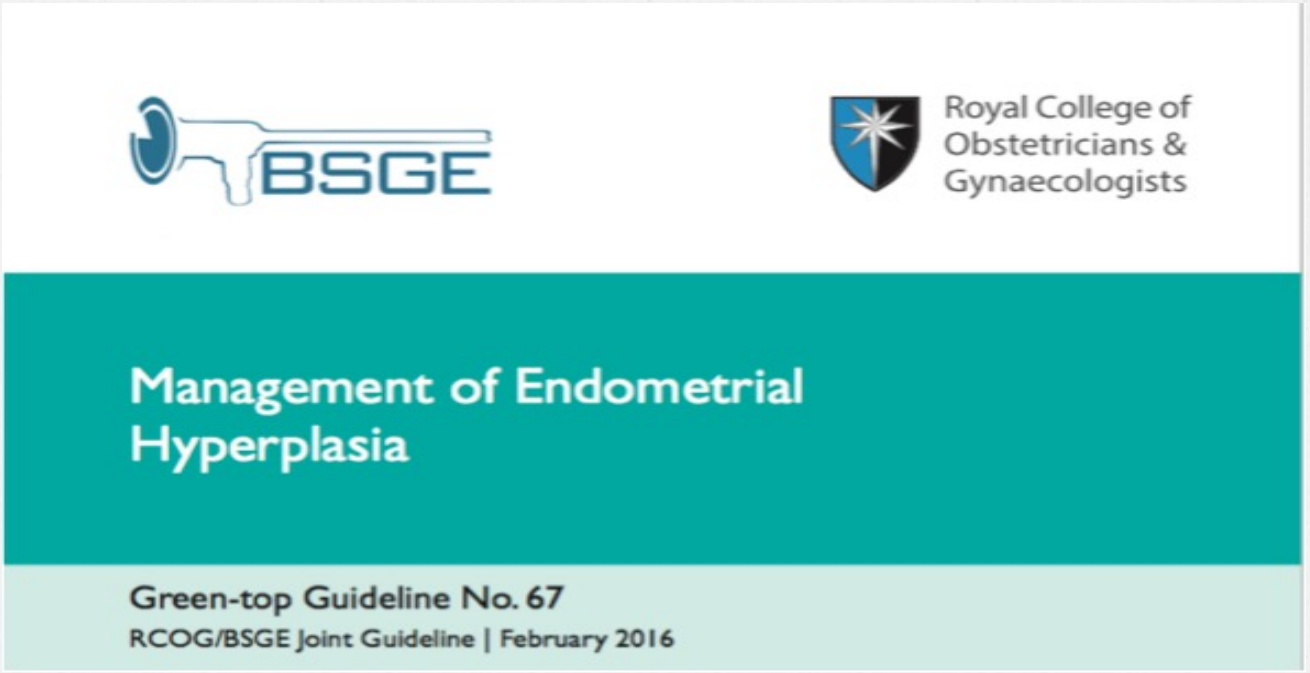
Early detection/screening (ACS 2015)

- There is no standard or routine screening test for women at average risk.
- Most cases (68%) are diagnosed at an early stage because of postmenopausal bleeding.
- Women are encouraged to report any unexpected bleeding or spotting to their physicians.

Early detection/screening (ACS 2015)

- ACS recommends that at the time of *menopause*, ALL women should be told about the risks and symptoms of endometrial cancer. Women should report any unexpected vaginal bleeding or spotting to their doctors.
- ACS recommends that women with known or suspected Lynch syndrome be offered annual screening with endometrial biopsy and/or trans-vaginal ultrasound beginning at age 35.

Endometrial hyperplasia evidence-based approach



Definition

it is irregular proliferation of the endometrial glands with an increase in the gland to stroma ratio when compared with proliferative endometrium.

Etiology

1- Endometrial hyperplasia develops when estrogen, unopposed by progesterone, stimulates endometrial cell growth by binding to estrogen receptors in the nuclei of endometrial cells.

2- other elements such as immunosuppression and infection may also be involved.

Clinical presentation

- The most common presentation of endometrial hyperplasia is *abnormal uterine bleeding*; includes
  - heavy menstrual bleeding,
  - inter-menstrual bleeding,
  - irregular bleeding,
  - unscheduled bleeding on HRT
  - postmenopausal bleeding

Classification

- **WHO 1994 :**

(i) simple hyperplasia,

(ii) complex hyperplasia,

(iii) Simple hyperplasia with atypia and

(iv) complex hyperplasia with atypia.

The association of cytological atypia with an increased risk of endometrial cancer has been known since 1985.

Classification

Endometrial intraepithelial neoplasia (EIN) classification (2003): NOT popular

The EIN diagnostic schema comprises 3

Categories :

1-benign (endometrial hyperplasia),

2- premalignant (a diagnosis of EIN based upon five subjective histological criteria) and

3- malignant (endometrial cancer)

Classification

The 2014 revised WHO classification:

- ***Simply separates endometrial hyperplasia into 2 groups based upon the presence or absence of cytological atypia,*** (i) hyperplasia without atypia and

(ii) atypical hyperplasia;

- The complexity of architecture is ***no longer*** part of the Classification.

[D]

The revised 2014 WHO classification of endometrial hyperplasia is recommended.

Classification systems for endometrial hyperplasia

WHO1994	EIN	European	WHO (modified)
Simple hyperplasia without atypia Complex hyperplasia without atypia	Hyperplasia	Hyperplasia	Hyperplasia without atypia
Simple hyperplasia with atypia Complex hyperplasia with atypia	EIN	Endometrial neoplasia	Hyperplasia with atypia Borderline
Carcinoma	Carcinoma		Carcinoma

WHO 1994 classification

Definition	Histology	Cytology	Rate of progression to cancer
Simple hyperplasia without atypia	• Endometrial glands predominately simple (tubular or cystic) structures • Minimal glandular crowding • Low gland:stroma ratio • Abundant intervening stroma between glands • Varying degrees of irregular branching with infoldings and outpouchings • Cells of columnar epithelium maintain orientation to underlying basement membrane	• Resembles normal proliferative endometrium but cells larger • Columnar cells • Amphophilic cytoplasm • Pseudostratified smooth oval nuclei • Nuclei maintain orientation to underlying basement membrane • Evenly dispersed chromatin • Small nucleoli • Variable number of mitoses	0.7–1.5%
Simple hyperplasia with atypia		• Nuclei ◦ Stratification with loss of polarity ◦ Enlarged, rounded with irregular shapes ◦ Coarsening of chromatin creating a vesicular appearance ◦ Prominent nucleoli ◦ Mitotic activity, variable amount • Cytoplasm ◦ Eosinophilia, diffuse or focal • Glands ◦ Often markedly increased gland-stroma ratio	3–8%
Complex hyperplasia without atypia	• Gland crowding with back to back position but with intervening stroma present • Gland:stroma ratio 2:1 • Structural complexity of glands including outpouchings, infoldings and budding	◦ Identical to simple hyperplasia without atypia	3–9%
Complex hyperplasia with atypia		◦ Identical to simple hyperplasia with atypia	20–30%

Diagnosis

- Histological examination via outpatient endometrial sampling [B]
- Diagnostic hysteroscopy should be considered if biopsy failed or non diagnostic, or endometrial hyperplasia has been diagnosed within a polyp or other discrete focal lesion. ☑
- Trans-vaginal ultrasound may have a role in diagnosing endometrial hyperplasia in pre- and postmenopausal women. ☑

Diagnosis

There is insufficient evidence evaluating (CT), (MRI) or biomarkers as aids in the management of endometrial hyperplasia and their use is not routinely recommended. [B]

MANAGEMENT

E H *without* a t y p ia

Initial counseling

- Women *should be informed* that the risk of EH without atypia progressing to endometrial cancer is less than 5% over 20 years and that the majority of cases of endometrial hyperplasia without atypia will regress spontaneously during follow-up. [B]

-Reversible risk factors such as obesity and the use of HRT should be identified and addressed if possible. ☑

E H *without* a t y p ia

initial counseling

Observation alone with follow-up endometrial biopsies to ensure disease regression can be considered,

especially when identifiable risk factors can be reversed.

However, women should be informed that

treatment with progestogens has a higher disease regression rate compared with observation alone.

[C]

E H without a t y p ia

Medical treatment;

is indicated in women who *fail* to regress following observation alone and in *symptomatic* women with abnormal uterine bleeding ☑

EH *without* atypia
Medical treatment;

- Progestogens ; Both continuous oral and local intrauterine (levonorgestrel-releasing intrauterine system [LNG-IUS]) are effective in achieving regression of endometrial hyperplasia without atypia [A]

EH *without* atypia

Medical treatment;

- The LNG-IUS should be the first-line medical treatment because compared with oral progestogens it has a higher disease *regression rate* with a more favorable bleeding profile and it is associated with fewer side effects. [A]

EH *without* atypia

Medical Treatment

Continuous progestogens should be used (medroxy-progesterone 10–20 mg/day **or** norethisterone 10–15 mg/day) for women who decline the LNG-IUS. [B]

EH *without* atypia

Medical Treatment

Cyclical progestogens should not be used because they are less effective in inducing regression of EH without atypia compared with continuous oral progestogens or the LNG-IUS [A]

EH *without* atypia

Duration of treatment and follow up

- Treatment with oral progestogens or the LNG-IUS should be for *a minimum of 6 months* in order to induce histological regression of endometrial hyperplasia without atypia. [B]

EH *without* atypia

Duration of treatment and follow up

If adverse effects are *tolerable* and fertility is *not* desired, women should be encouraged to retain the LNG-IUS *for up to 5 years* as this reduces the risk of relapse, especially if it alleviates abnormal uterine bleeding symptoms. ☑

EH *without* atypia

Duration of treatment and follow up

- Outpatient endometrial biopsy is recommended after a diagnosis of hyperplasia without atypia. [C]

- Endometrial surveillance should be arranged at a *minimum of 6-monthly intervals*. At least two consecutive 6-monthly negative biopsies should be obtained prior to discharge. [D]

EH *without* atypia

Duration of treatment and follow up

In women at higher risk of relapse, such as women with a BMI of ≥ 35 or those treated with oral progestogens, 6-monthly endometrial biopsies are recommended. Once two consecutive negative endometrial biopsies have been obtained then long-term follow-up should be considered with annual endometrial biopsies [D]

EH *without* atypia

Surgical management

- Hysterectomy should not be considered as a first-line treatment for hyperplasia without atypia as most cases respond to progestogens [C]
- Hysterectomy is indicated in women not wanting to preserve their fertility when: [C]

(1) progression to atypical hyperplasia occurs during follow-up,
(2) no histological regression of hyperplasia in 12 ms. treatment, (3) there is relapse of endometrial hyperplasia after treatment
(4) persistence of bleeding symptoms,
(5) the woman not compliant to progestogen or follow-up .

EH *without* atypia
Surgical management

- Postmenopausal women ; *should be offered a bilateral salpingo-oophorectomy* together with total hysterectomy. ☑
- For pre-menopausal women, the decision to remove the ovaries *should be individualised*; however, bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy. [D]

EH *without* atypia

Surgical management

- Endometrial ablation is not recommended for the treatment of endometrial hyperplasia because:

- complete endometrial destruction not ensured

- resulting adhesion perclude future endometrial surveillance [D]

EH *with* Atypia

Surgical management

A laparoscopic approach to total hysterectomy is preferable to an abdominal approach as it is associated with a shorter hospital stay, less postoperative pain and quicker recovery. [B]

EH *with* Atypia
Surgical management

- No benefit from intraoperative *frozen section* analysis of the endometrium or routine lymphadectomy. [C]

- Post-menopausal women with atypical hyperplasia should be offered bilateral salpingo-oophorectomy together with the total hysterectomy. ☑

EH *with* Atypia
Surgical management

- For **pre**menopausal women, the decision to remove the ovaries should be individualized; however,

bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy. [D]

- Endometrial ablation is not recommended because of the same reasons mentioned before. [C]

EH with Atypia

women wishing fertility or unsuitable for surgery

MANAGEMENT

- Should be counseled about the risks of underlying malignancy & subsequent progression to endometrial cancer. ☑
- Pretreatment investigations should aim to rule out invasive endometrial cancer or co-existing ovarian cancer. ☑

Special cases

- *Women wishing fertility or unsuitable for surgery.*
- *EH & fertility management*
- *EH & HRT*
- EH- in women on adjuvant treatment for breast cancer

EH *with* Atypia

Women wishing fertility or unsuitable for surgery

MANAGGEMENT

- *First-line* treatment with the LNG-IUS should be recommended, with oral progestogens as a second-best alternative . [B]

- Once fertility is no longer required, hysterectomy should be offered in view of the high risk of relapse. [B]

EH *with* Atypia

Women Not undergoing hysterectomy

FOLLOW UP

- Routine endometrial biopsies every 3 month until 2 consecutive negative endometrial biopsies obtained [D]

- For asymptomatic women with 2 negative endometrial biopsies --- Long term follow up with 6-12 months biopsy until hysterectomy is performed ☑

EH and fertility management

- Disease regression should be achieved on at least one endometrial sample before women attempt to conceive. ☑
- Assisted reproduction may be considered as the live birth rate is higher and it may prevent relapse compared with women who attempt natural conception. **[C]**
- Regression of endometrial hyperplasia should be achieved before ART as this is associated with higher implantation and clinical pregnancy rates. [B]

EH and HRT

- **Systemic estrogen-only HRT should not be used in women with a uterus. [A]**
- **All women taking HRT should be encouraged to report any unscheduled vaginal bleeding promptly. ☑**
- **women on sequential HRT preparation and wishing to continue HRT are advised to shift to LNG-IUS or a continuous combined HRT preparation [B]**

EH- in women on adjuvant treatment for breast cancer

- Women taking tamoxifen should be informed about the increased risks of developing endometrial hyperplasia and cancer. They should be encouraged to report any abnormal vaginal bleeding or discharge promptly. [D]

- Women taking aromatase inhibitors (such as anastrozole, exemestane and letrozole) should be informed that these medications are not known to increase the risk of endometrial hyperplasia and cancer. ☑

EH- in women on adjuvant treatment for breast cancer

There is evidence that the LNG-IUS prevents polyp formation and that it reduces the incidence of endometrial hyperplasia in women on tamoxifen. The effect of the LNG-IUS on breast cancer recurrence risk remains uncertain so its routine use cannot be recommended.

[A]

EH- in women on adjuvant treatment for breast cancer

- Endometrial hyperplasia confined to an endometrial polyp, complete removal of uterine polyp (s) is recommended & endometrial biopsy should be obtained to sample the background endometrium [D]

- Subsequent management according to the histological classification of EH ☑

THANK YOU FOR ATTENSION