Endometrial Hyperplasia&Cancer

Dr. Mousavi

Naigo webinar

Introduction

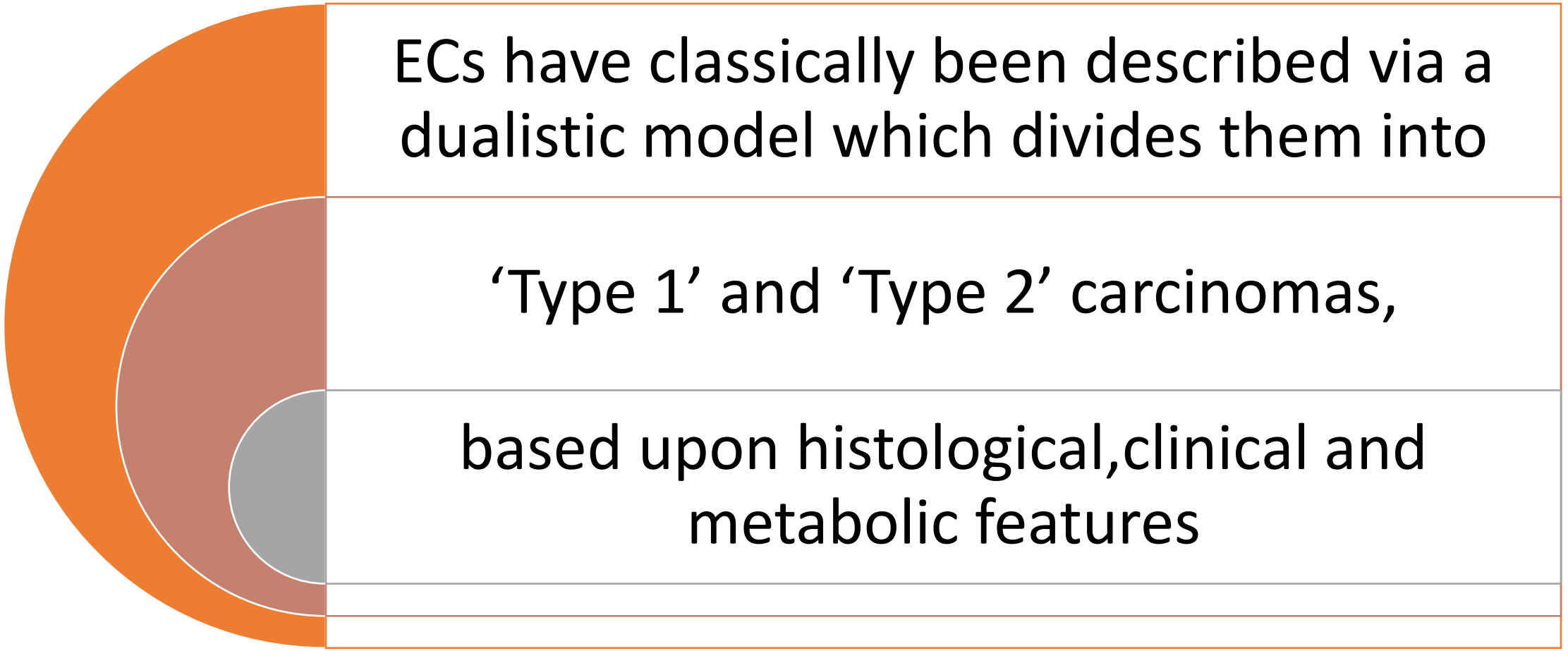
Endometrial cancer (EC) is the most common gynaecological malignancy affecting women in developed countries and the second most common gynaecological malignancy world-wide, due to the higher rates of cervical cancer in the developing world

Endometrial cancer

- If diagnosed and treated at FIGO Stage I or II 5-year survival figures stand at ~92% and 75%

- . Women diagnosed with advanced EC, FIGO stages III and IV, have 5-year survival figures reported at 57–66% and 20–26%,

Endometrial Cancer



Type 1

The Type 1 carcinomas, of which the endometrioid histological subtype accounts for ~75%

, typically low-grade tumors which are often amenable to surgical treatment .

Type 1 ECs are considered oestrogen-dependent and are frequently associated with hyperplastic proliferation of the endometrial glands

they are characteristically seen in postmenopausal obese women.

Type 2

Type 2 ECs tend to be oestrogen-independent

include the clinically aggressive ‘serous’ and ‘clear cell’ histological subtypes.

Type 2 ECs are more often associated with endometrial atrophy in the postmenopausal woman rather than with endometrial hyperplasia

- They are linked with a much poorer clinical prognosis

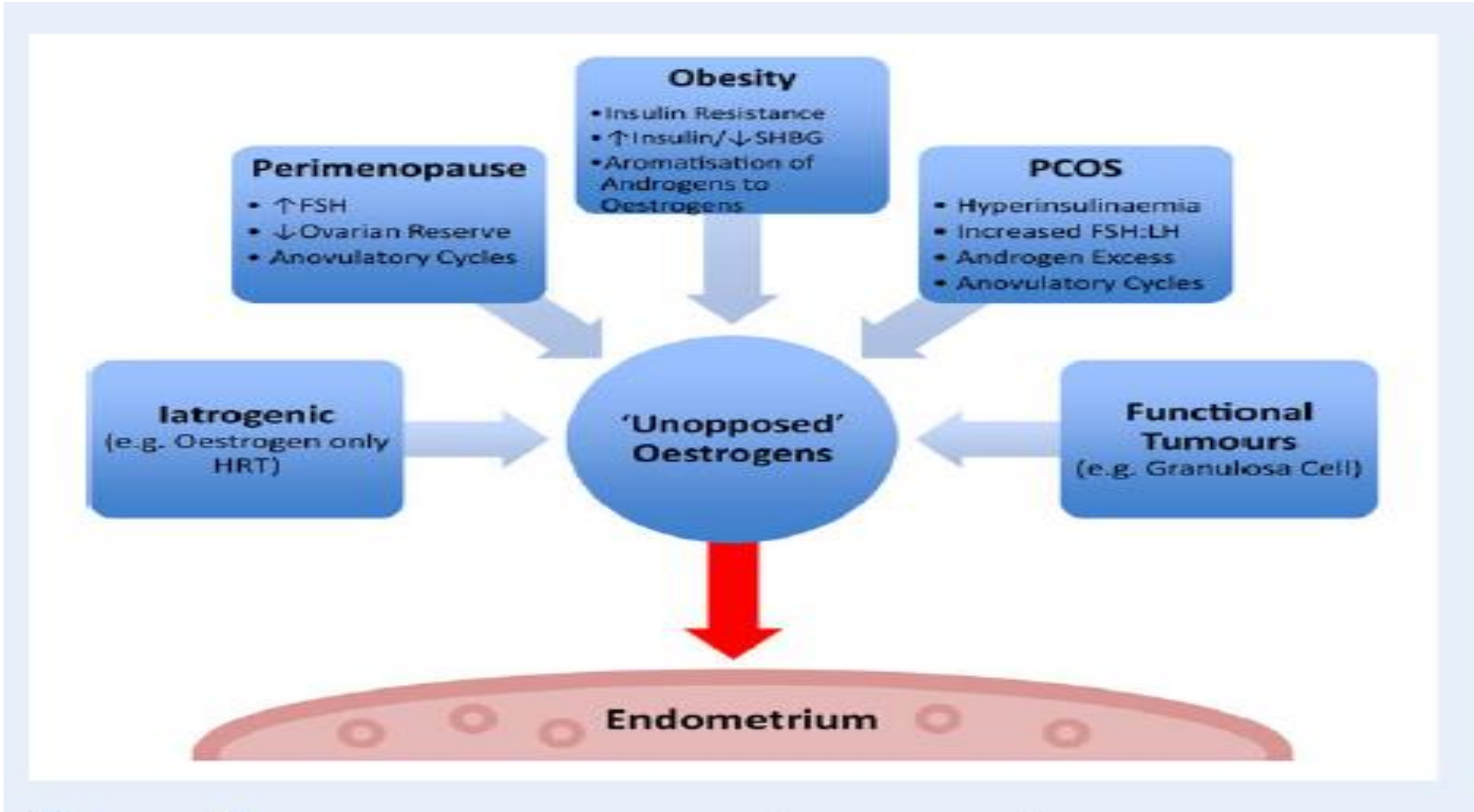
Endometrial Hyperplasia

- The endometrium, the innermost glandular layer of the uterus, is a dynamic tissue that goes through a series of alterations (proliferation, secretion and menstruation/shedding) during the menstrual cycle in a woman’s reproductive years .

- This cyclic phase involves a complex interaction between the two female sex hormones, estradiol, and progesterone

Endometrial hyperplasia

Endometrial hyperplasia (EH) is a pre-cancerous, non-physiological, non-invasive proliferation of the endometrium that results in increased volume of endometrial tissue with alterations of glandular architecture (shape and size) and endometrial gland to stroma ratio of greater than 1:1


Obesity
•Insulin Resistance
•↑Insulin/↓SHBG
•Aromatisation of Androgens to Oestrogens
Perimenopause
• ↑FSH
• ↓Ovarian Reserve
• Anovulatory Cycles
PCOS
• Hyperinsulinaemia
• Increased FSH:LH
• Androgen Excess
• Anovulatory Cycles
Iatrogenic
(e.g. Oestrogen only HRT)
'Unopposed' Oestrogens
Functional Tumours
(e.g. Granulosa Cell)
Endometrium

Classification of EH WHO1994

WHO94 categories	Histological and cytological features
Simple hyperplasia without atypia (SH)	• Irregularly shaped and sized glands • Cystic dilatation • Abundant cellular stroma • No back to back crowding • Nuclear pseudo-stratified glands but no nuclear atypia • Variable mitotic activity
Simple atypical hyperplasia (SAH)	• As per SH including nuclear atypia
Complex hyperplasia without atypia (CH)	• Crowded glands—can be complex or tubular, with or without dilatation • Sparse intervening stroma • Oval, bland nuclei with uniform shape • Variable mitotic activity
Complex atypical hyperplasia (CAH)	• Tightly packed glands • Very little intervening stroma • Nuclear atypia

WHO 2014 Classification

- The 2014 WHO endometrial hyperplasia classification system has only two categories :
- Hyperplasia without atypia (non-neoplastic)

- Atypical hyperplasia (endometrial intraepithelial neoplasm)

Endometrial intraepithelial neoplasia classification(EIN)

- The endometrial intraepithelial neoplasia (EIN) classification system was proposed by an international group of gynecologic pathologists in 2000

The EIN system defines two classes of endometrial changes:

- Benign endometrial hyperplasia (EH, non-neoplastic) – Changes typically observed with anovulation or other etiology of prolonged exposure to estrogen.

- Endometrial intraepithelial neoplasia (EIN) – Endometrial precancers.

Concurrent Endometrial Carcinoma in Women with a Biopsy Diagnosis of Atypical Endometrial Hyperplasia

A Gynecologic Oncology Group Study

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BACKGROUND. Adenocarcinoma of the endometrium is the most common gynecologic malignancy in the United States, accounting for approximately 36,000 diagnoses of invasive carcinoma annually. The most common histologic type, endometrioid adenocarcinoma (EC), accounts for 75–80% of patients. The objective of this work was to estimate the prevalence of concurrent carcinoma in women with a biopsy diagnosis of the precursor lesion, atypical endometrial hyperplasia (AEH).

METHODS. This prospective cohort study included women who had a community diagnosis of AEH. Diagnostic biopsy specimens were reviewed independently by three gynecologic pathologists who used International Society of Gynecologic Pathologists/World Health Organization criteria. Study participants underwent hysterectomy within 12 weeks of entry onto protocol without interval treatment. The hysterectomy slides also were reviewed by the study pathologists, and their findings were used in the subsequent analyses.

RESULTS. Between November 1998 and June 2003, 306 women were enrolled on

- These issues were highlighted by Trimble et al.
- in a study in which 289 endometrial specimens with a diagnosis of atypical EH were re-reviewed by specialize gynaecological pathologists using WHO94 criteria;
- 25% of cases were downgraded to a less severe histology than atypical EH
- and 29% were upgraded to EC

Diagnosis

Women who should undergo evaluation for endometrial hyperplasia or endometrial cancer

1-Abnormal uterine bleeding

Postmenopausal women – Any uterine bleeding, regardless of volume

Age 45 years to menopause – In any woman, bleeding that is frequent (interval between the onset of bleeding episodes is <21 days), heavy, or prolonged (>5 days) or intermenstrual bleeding

Younger than 45 years – Any abnormal uterine bleeding in obese women (BMI ≥30).

In nonobese women, abnormal uterine bleeding that is persistent and occurs in the setting of one of the following: chronic ovulatory dysfunction, other exposure to estrogen unopposed by progesterone, failed medical management of the bleeding, or women at high risk of endometrial cancer (eg, Lynch syndrome, Cowden syndrome).

2-EH

In addition, endometrial neoplasia should be suspected in premenopausal women who are anovulatory and have prolonged periods of amenorrhea (six or more months).

3-Cervical cytology results

•Presence of AGC-endometrial.
•Presence of AGC-all subcategories other than endometrial – If ≥35 years of age OR at risk for endometrial cancer (risk factors or symptoms).
•Presence of benign-appearing endometrial cells in women ≥40 years of age who also have abnormal uterine bleeding or risk factors for endometrial cancer.

Other Indication

•Monitoring of women with endometrial pathology (eg, endometrial hyperplasia).
•Screening in women at high risk of endometrial cancer (eg, Lynch syndrome).

The American Cancer Society recommends that annual screening for endometrial cancer with endometrial biopsy should be offered by age 35 for women with or at risk for hereditary nonpolyposis colorectal cancer (HNPCC).

Precancer Diagnosis: Endometrial Sampling

A 2000 meta-analysis of 39 studies involving 7914 women compared the results of endometrial sampling with histopathology at D&C, hysteroscopy, and/or hysterectomy . The significant findings from this analysis were:

Endometrial Biopsy

- The Pipelle device was more sensitive for the detection of endometrial cancer and atypical hyperplasia than all other sampling devices.
- The sensitivity for the diagnosis of endometrial cancer (by Pipelle) in postmenopausal women was 99.6 percent and in premenopausal women was 91 percent.
- The sensitivity for the diagnosis of atypical endometrial hyperplasia was 81 percent.
- The specificity for all endometrial biopsy devices for the diagnosis of endometrial carcinoma was 98 to 100 percent.
- Fewer than 5 percent of patients had an insufficient or no sample.

Indication for D&C

- When a patient is not able to tolerate an office endometrial biopsy (eg, due to pain or anxiety).
- After a nondiagnostic office biopsy in women who are at high risk of endometrial carcinoma.
- When TVUS suggests a suspicious mass or polyp, which may not be adequately sampled by office biopsy.
- After benign histology on office biopsy in women who have persistent abnormal uterine bleeding.
- When there is insufficient tissue for analysis on office biopsy.
- When cervical stenosis prevents the completion of an office biopsy.
- When a concomitant operative procedure, such as laparoscopy, is deemed necessary.

Diagnostic hysteroscopy

- Diagnostic hysteroscopy provides direct visualization of the endometrial cavity, thereby allowing targeted biopsy or excision of lesions identified during the procedure
- For patients at risk for endometrial cancer who are candidates for D&C, we advise performing a diagnostic hysteroscopy at the time of D&C. This approach is consistent with guidelines from the Society of Gynecologic Oncology
- Curettage should be taken of the background endometrium
- A meta-analysis of observational studies reported no significant difference in the frequency of positive peritoneal cytology in women with endometrial carcinoma who had or had not undergone diagnostic hysteroscopy

Hysteroscopy with directed biopsy is more sensitive than D&C in the diagnosis of uterine lesions

NONINVASIVE TECHNIQUES

Diagnosis of Endometrial Cancer Among Women With Postmenopausal Bleeding ACOG

- Transvaginal ultrasonography has excellent negative predictive value for endometrial cancer in women with postmenopausal bleeding.

- When transvaginal ultrasonography is performed for patients with postmenopausal bleeding and an endometrial thickness of 4 mm or less is found, endometrial sampling is not required because of the very low risk of uterine malignancy in these patients

TVS

- In addition, ACOG advises that TVUS is useful as a second-line test when endometrial sampling yielded insufficient tissue.

- In such cases, they advised that if the endometrial thickness is ≤4 mm, then malignancy is rare.

- In addition, ultrasound may identify a structural lesion (eg, polyp).

SUMMARY AND RECOMMENDATIONS

- **Initial evaluation**
- Endometrial biopsy is preferred initial test for women with abnormal uterine bleeding due to its high sensitivity, low complication rate, and low cost.
- Transvaginal pelvic ultrasound is an acceptable alternative initial test in postmenopausal women who cannot tolerate office biopsy, or in women who need concurrent evaluation of the adnexae.
- Endometrial cutoff of ≤4 mm would yield a false-negative rate for endometrial cancer of 0.25 to 0.5 percent, which compares favorably with the false-negative rate reported for endometrial biopsy.
- For patients evaluated with pelvic ultrasound, endometrial biopsy is required for histological diagnosis if the endometrium is not adequately visualized, the endometrial stripe thicker than 4 mm (focal or global), and in women with persistent bleeding.
- Blind biopsy is most accurate in women with a globally thickened endometrium; visually directed sampling (ie, hysteroscopy) is preferable for women with focal abnormalities.

Evaluation of persistent bleeding

- Persistent abnormal bleeding in peri- or postmenopausal women is worrisome even with a benign or negative initial evaluation.
- Persistent bleeding is worrisome even when the endometrial thickness is <4 mm, particularly if there are other risk factors for endometrial cancer .
- Endometrial cancer can still occur in this setting since serous carcinoma of the endometrium may arise from atrophic endometrium. Therefore, further diagnostic evaluation is indicated.
- Evaluation for a nonendometrial source of bleeding, such as cervical, fallopian tube, or ovarian cancer, should also be pursued

Asymptomatic women with endometrial thickening or fluid

postmenopausal women without uterine bleeding who had an endometrial thickness >11 mm had an endometrial cancer risk of 6.7 percent

which is similar to that in postmenopausal women with bleeding and endometrial thickness >5 mm .

Based on this analysis, we suggest sampling the endometrium of postmenopausal women without uterine bleeding who have an endometrial thickness >11 mm.

Endometrial Fluid

- Observational studies have consistently found that asymptomatic postmenopausal women with endometrial fluid and an endometrial thickness smaller than 3 mm do not have endometrial cancer or hyperplasia .
- However, there is an increased risk of endometrial cancer in women with endometrial fluid and endometrial thickening >3 mm; therefore, we biopsy these women

MANAGEMENT OPTIONS :Endometrial Hyperplasia

The three most common options for the management of EH are

Surveillance

Progestin therapy

Hysterectomy.

Other treatments — Endometrial Hyperplasia

Treatment with nonprogestin medications or conservative surgery is not standard clinical practice, but has been described

PROGESTIN THERAPY ADMINISTRATION

Progestins reverse EH by activation of progesterone receptors, which results in stromal decidualization and subsequent thinning of the endometrium.

Progestin exposure also decreases estrogen effect by activate hydroxylase enzymes to convert estradiol to its less active metabolite estrone

Contraindications — Contraindications to progestin therapy include:

- Current or past history of thromboembolic disorders, or stroke
- Severe liver dysfunction
- Known or suspected malignancy of progesterone receptor-positive breast cancer
- Vaginal bleeding of unknown etiology
- Pregnancy
- Known allergic reaction to progestins

Medications, routes, and outcomes

Historically, the most common treatments were oral medroxyprogesterone acetate (MPA) or megestrol acetate, but

The LNG-releasing IUD, 52 mg with a release rate of 20 mcg/day over five years (Mirena; LNG 52), is now first-line therapy.

Oral progestin

- Megestrol acetate 40 to 160 mg daily
- MPA 10-20 mg daily
- Norethindrone acetate (NETA; also known as norethisterone acetate) 15 mg daily
- Micronized progesterone 200 to 300 mg daily
- regimen for treating EH, continuous (daily dosing) progestins or progestin IUDs are superior to cyclic progestin regimens

Nonprogestin medications

Gonadotropin-releasing hormone (GnRH) agonists

Aromatase Inhibitors

Ovulation induction (eg, with clomiphene or aromatase inhibitors) in reproductive-age women

Metformin

Alternative surgical treatments

Hysteroscopic resection of EH was reported to be effective in 68 of 73 treated women, but the long-term consequence of this treatment remains to be determined

Bariatric surgery may show promise

Follow-up

— Every woman with EH requires careful follow-up and appropriate surveillance for persistent or recurrent EH or progression to carcinoma, regardless of type.

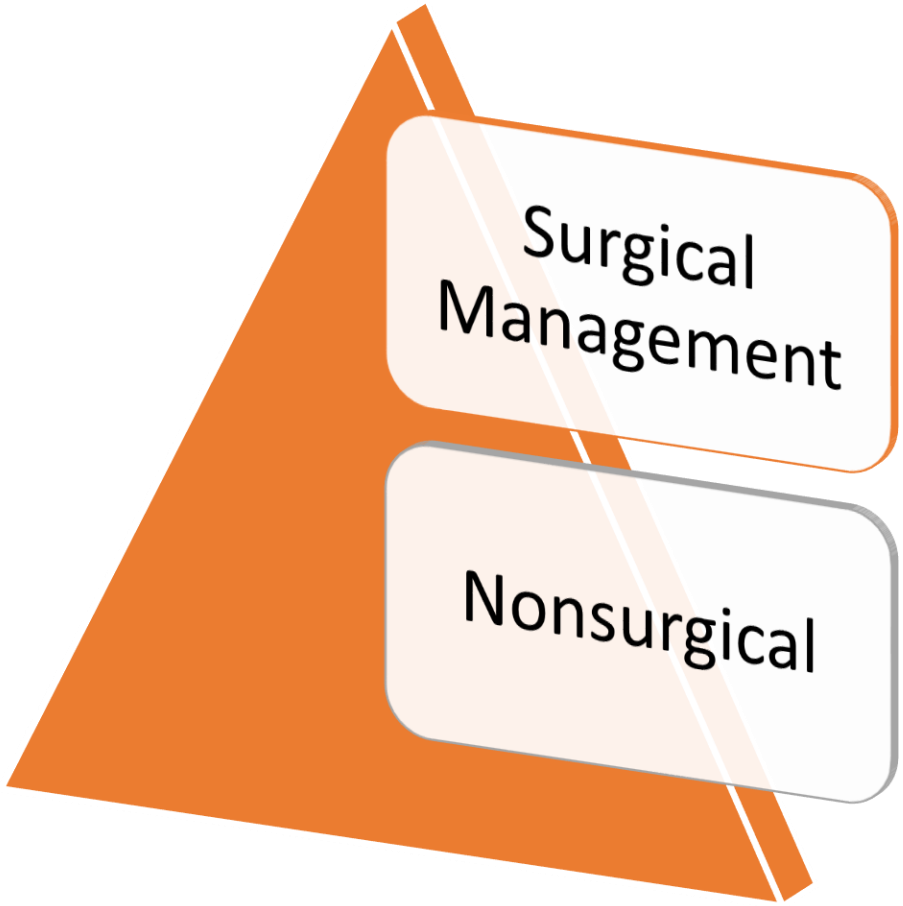
F/U

- For **premenopausal women** with simple EH without atypia, if the menstrual pattern normalize, repeat endometrial biopsy is not required.
- However, if the bleeding pattern does not normalize,D&C preferly with hysterescopy is indicated after TVS
- ●For **postmenopausal women** with simple EH without atypia who are treated with progestins, repeat the endometrial biopsy every three to six months.

Management of Endometrial Intraepithelial Neoplasia

- The primary objectives in a patient in whom endometrial intraepithelial neoplasia has been newly diagnosed are the following:

- Ruling out a concurrent adenocarcinoma
- Designing a treatment plan
- Preventing the progression to endometrial cancer.


Surgical Management
Nonsurgical

Surgical Assessment and Management Options

- When clinically appropriate, total hysterectomy for endometrial intraepithelial neoplasia provides definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions .

- Current surgical options include abdominal, vaginal, and minimally invasive procedures.

- These methods are acceptable to perform a hysterectomy with or without bilateral salpingo-oophorectomy in patients with a biopsy diagnosis of endometrial intraepithelial neoplasia.
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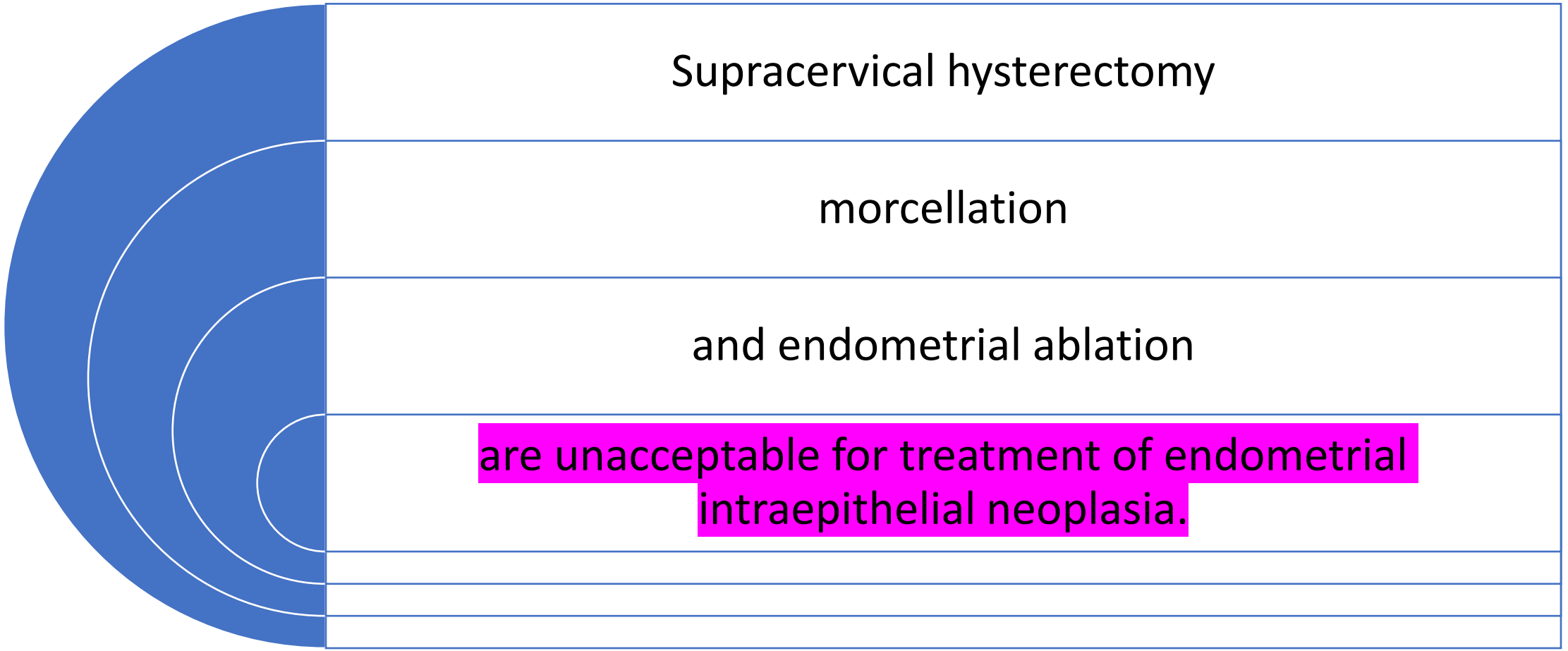
EIN TREATMENT



The scope of the operation may be changed based on intraoperative assessment and pathologic review. Evaluation could include opening the specimen to assess for gross evidence of a tumor or myoinvasion

For patients with endometrial hyperplasia planned for hysterectomy and who have not had a D&C, a pathologist should be available to evaluate if the intraoperative findings suggest endometrial carcinoma, and the ability to perform surgical staging should be considered.

Frozen Section

The correlation between frozen section and final pathology for histology, grade, and depth of myometrial invasion is approximately 97.5%, 88%, and 98.2%, respectively .

Furthermore, high-risk disease is identified more efficiently in frozen section compared with low-risk disease

EIN

Total hysterectomy, salpingectomy with or without oophorectomy, along with peritoneal washings, may be the most appropriate surgical treatment for endometrial intraepithelial neoplasia,

Nonsurgical Management Options

- Nonsurgical management is acceptable for patients who
- desire future fertility
- or patients with sufficient medical comorbidities precluding surgical management.
- The therapeutic goals for patients who desire future fertility are complete clearance of disease, reversion to normal endometrial function, and prevention of invasive adenocarcinoma.
- Current nonsurgical management options are limited to hormonal therapy.

For women with a diagnosis on office endometrial biopsy of atypical endometrial hyperplasia who desire medical management, perform a D&C to exclude endometrial carcinoma.

Hormonal Treatment for Endometrial Intraepithelial Neoplasia

Systemic or local progestin therapy is an unproven but commonly used alternative to hysterectomy that may be appropriate for women who are poor surgical candidates or who desire to retain fertility.

A systematic review and meta-analysis found a pooled regression rate of 69% (95% confidence interval, 58–83) in 14 studies (n=189) of women with atypical hyperplasia treated with oral progestins. Pooling the seven studies (n=36) of women with atypical hyperplasia treated with the levonorgestrel IUD found a regression rate of 90% (95% confidence interval, 62–100)

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Review article

Efficacy of the LNG-IUS for treatment of endometrial hyperplasia and early stage endometrial cancer: Can biomarkers predict response?

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Author	Type of study	Number of participants	EC/ Hyperplasia	Response Rate
Pal et al., 2018	Retrospective study	n = 15	Hyperplasia	80%
Baker et al., 2017	Retrospective study	n = 46	Hyperplasia	80%
Marnach et al., 2016	Retrospective study	n = 94	Hyperplasia	87%
Sletten et al., 2018	Prospective study	n = 21	Hyperplasia	100%
Westin et al., 2020	Prospective study	n = 36	Hyperplasia	90.6%
Leone Roberti Maggiore et al., 2019	Prospective long term follow up study	n = 28	Hyperplasia	89.3%
Varma et al., 2008	Prospective long term follow up study	n = 105	Hyperplasia	90%
Wildemeersch et al., 2007	Prospective long term follow up study	n = 20	Hyperplasia	95%

Studies investigating the efficacy of LNG-IUS treatment of endometrial hyperplasia&EC

Scarselli et al., 2011	Prospective long term follow up study	n = 34	Hyperplasia	85%
Orbo et al., 2014	Randomised trial	n = 170	Hyperplasia	100%
Abu Hashim et al., 2015	Randomised trial	n = 59	Hyperplasia	67.8%
Gallos et al., 2013	Comparative cohort study	n = 250	Hyperplasia	94.8%
Westin et al., 2020	Prospective study	n = 21	Grade I EC	66.7%
Leone Roberti Maggiore et al., 2019	Prospective long term follow up study	Grade 1 EC: n = 16 Grade 2 EC: n = 4	Grade 1 EC Grade 2 EC	Grade 1 EC: 81.3% Grade 2 EC: 75%
Pal et al., 2018	Retrospective study	Grade 1 EC: n = 9 Grade 2 EC: n = 8	Grade 1 EC Grade 2 EC	Grade 1 EC: 67% Grade 2 EC: 75%

Hormonal Treatment For EIN

High dose progestron:

160 mg Megestrol

Conclusions and Recommendations

American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology make the following consensus recommendations:

The endometrial intraepithelial neoplasia schema seems to be preferable to the 1994 four-class World Health Organization (WHO94) schema.

The preferred terminology is “endometrial intraepithelial neoplasia” (rather than “atypical endometrial hyperplasia”).

Regarding tissue sampling, hysteroscopy, while not required, is recommended with directed dilation and curettage (D&C) to include any discrete lesions as well as the background endometrium.

When clinically appropriate, total hysterectomy for endometrial intraepithelial neoplasia provides definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions.

Supracervical hysterectomy, morcellation, and endometrial ablation are unacceptable for treatment of endometrial intraepithelial neoplasia.

Systemic or local progestin therapy is an unproven but commonly used alternative to hysterectomy that may be appropriate for women who are poor surgical candidates or who desire to retain fertility.

Follow-up during progestin therapy for atypical EH includes: premenopausl

Post hormonal treatment surveillance after nonsurgical management of endometrial intraepithelial neoplasia may include serial endometrial sampling every 3–6 months, but the appropriate frequency has not yet been determined.

For **postmenopausal women** who are not surgical candidates:

- transvaginal ultrasound or endometrial sampling every six months for one to two years.

- If abnormal transvaginal ultrasound findings (endometrial thickness >4 mm) are found, hysteroscopy and dilation and curettage should be performed.

- Maintenance therapy with progestin

Postmenopausal women with no known estrogen source

- Endometrial hyperplasia with or without atypia in a woman who should be estrogen-deficient requires an explanation.

- In the absence of other sources of estrogen (eg, estrogen therapy, obesity), such women require evaluation for an estrogen-producing tumor.


thank
you