Classification & Management Of Endometrial Hyperplasia Update

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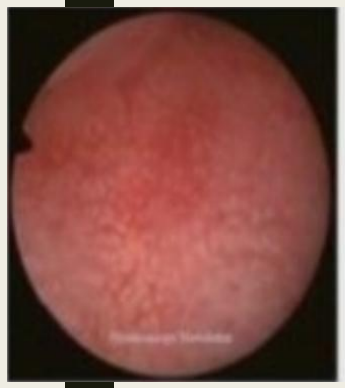
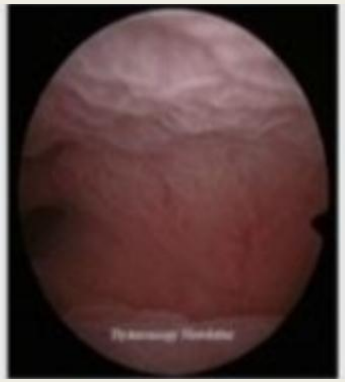
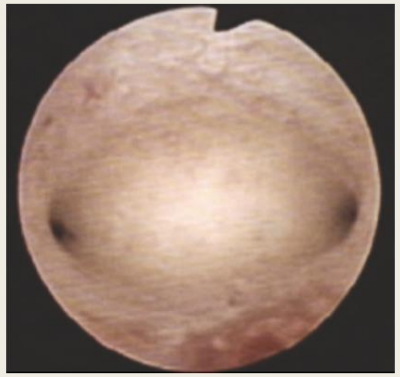
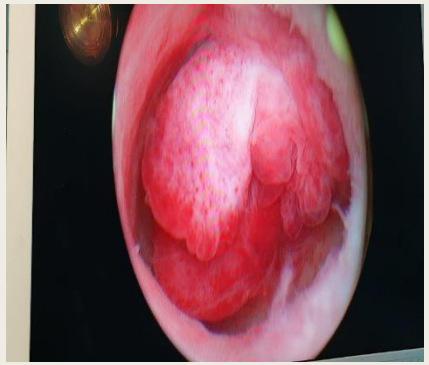
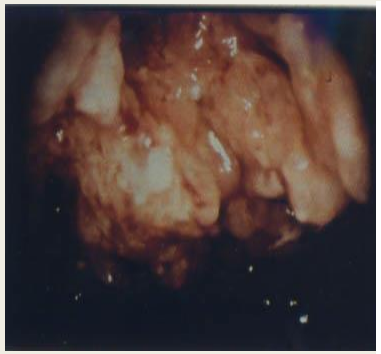
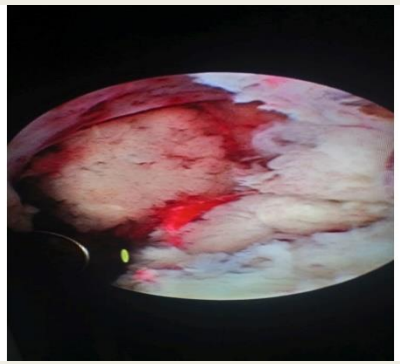
DISCLOSURE

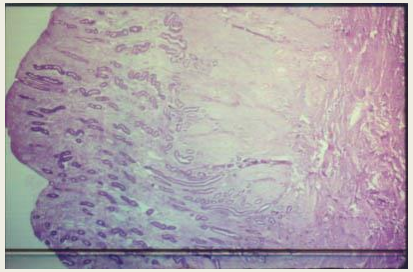
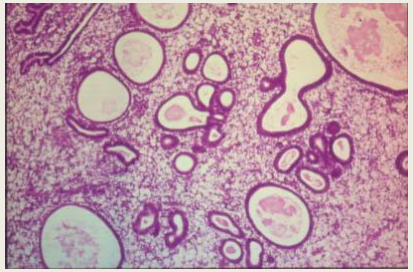
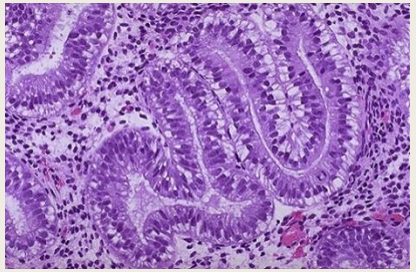
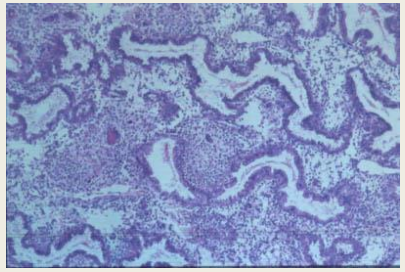
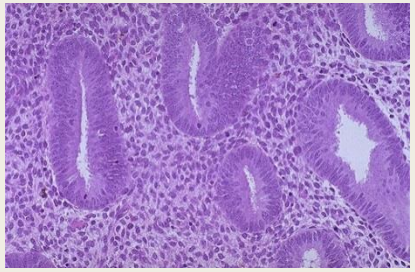
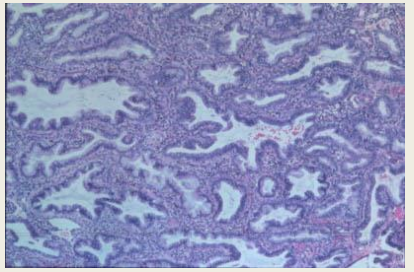
Postmenopausal Bleeding

Cause of Bleeding	Frequency
Endometrial atrophy	60 – 80
Estrogen replacement therapy	15 – 25
Endometrial polyps	2 – 12
Endometrial hyperplasia	5 – 10
Endometrial cancer	10

■ Endometrial Hyperplasia

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

■ Endometrial Hyperplasia

- 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

■ Endometrial Hyperplasia Clinical Presentation

- Abnormal uterine bleeding; includes - heavy menstrual bleeding, - inter - menstrual bleeding, - irregular bleeding.
- Unscheduled bleeding on HRT.
- Postmenopausal bleeding.

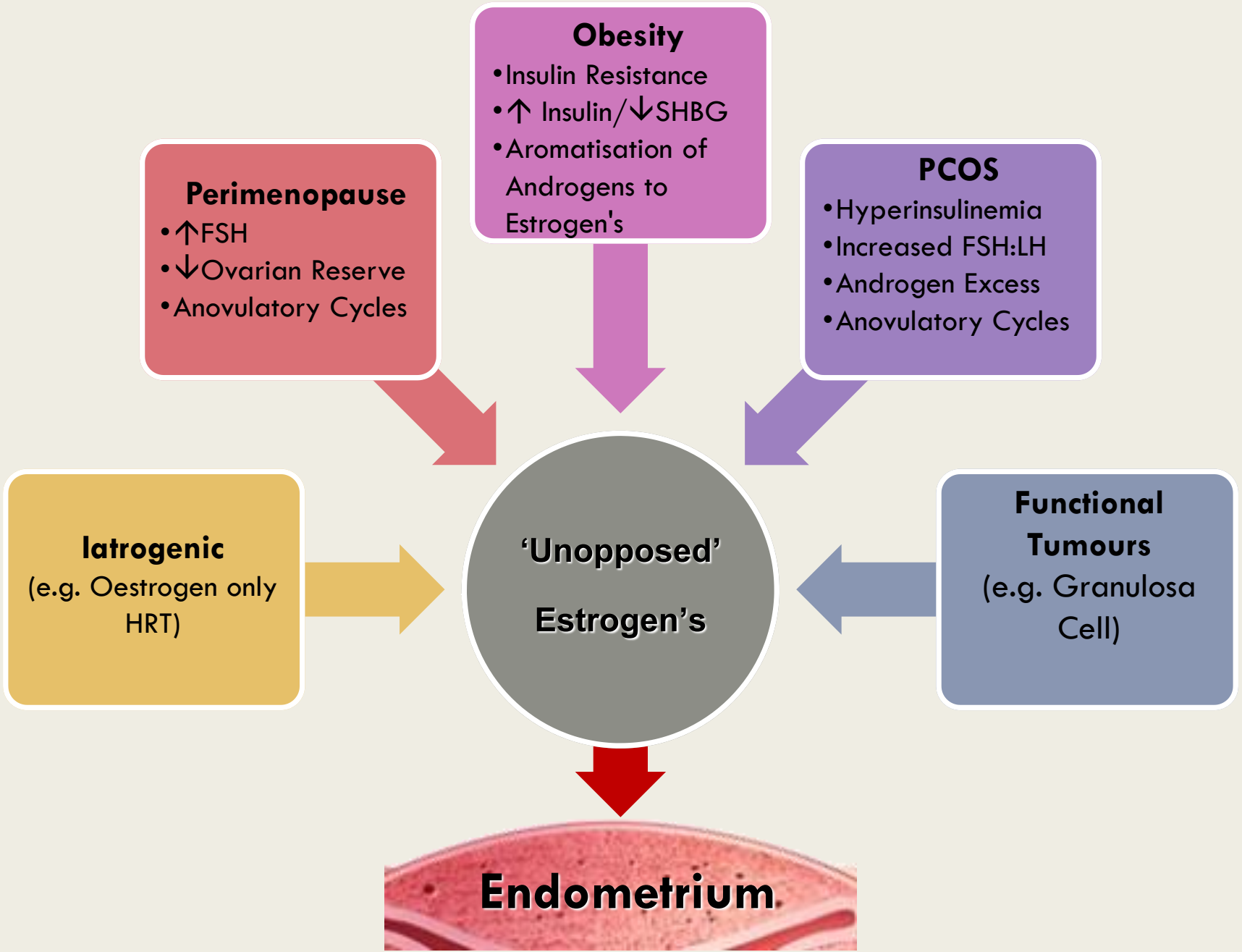
■ What are the Risk Factors for Endometrial Hyperplasia?

Endometrial hyperplasia is often associated with multiple identifiable risk factors and assessment should aim to identify and monitor these factors.

■ Risk factors for the development of endometrial hyperplasia (EH).

Risk factor category	Risk factor
Non-modifiable	Age >35 years Caucasian ethnicity Family history
Menstrual	Postmenopausal status Early menarche/late menopause Prolonged perimenopause Null parity
Co-morbid conditions	Obesity Diabetes mellitus Polycystic ovarian syndrome (PCOS) Functional tumours, e.g. granulosa cell Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC)
Iatrogenic	Long-term Tamoxifen therapy Oestrogen only hormone replacement therapy (HRT) Exogenous oestrogen exposure
Others	Smoking Genetic mutations

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


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

■ Pathogenesis of Endometrial hyperplasia

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

■ Endometrial Hyperplasia

Type of Hyperplasia	Progression to Cancer (%)
Simple (Cystic without atypia)	1
Complex (adenomatous without Atypia)	3
Simple (Cystic without atypia)	8
Complex (adenomatous with atypia)	29

Kurman RJ, Kaminski PF, Norris HJ. 170 patient. *Cancer 1985;56:403–12.*

New Classification WHO 2014 of Endometrial Hyperplasia

New term	Synonyms	Genetic changes	Coexistent invasive endometrial carcinoma	Progression to invasive carcinoma
Hyperplasia *without* atypia	Benign endometrial hyperplasia; simple non-atypical endometrial hyperplasia; complex non-atypical endometrial hyperplasia; simple endometrial hyperplasia without atypia; complex endometrial hyperplasia without atypia	Low level of somatic mutations in scattered glands with morphology on HE staining showing no changes	<1%	RR: 1.01–1.03
Atypical hyperplasia/endometrioid intraepithelial neoplasia	Complex atypical endometrial hyperplasia; simple atypical endometrial hyperplasia; endometrial intraepithelial neoplasia (EIN)	Many of the genetic changes typical for endometrioid endometrial cancer are present, including: micro satellite instability; *PAX2* inactivation; mutation of *PTEN*, *KRAS* and *CTNNB1*	25–33% 5 59% 3	RR: 14–45

■ Diagnosis & Management (Evidence Base Medicine)

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

What Diagnostic & Surveillance Methods & Available for Endometrial Hyperplasia?

Diagnosis of endometrial hyperplasia requires histological examination of the endometrial tissue. Endometrial surveillance should include endometrial sampling by outpatient endometrial biopsy. B

Many expert recommend hysteroscopy and biopsy in case of atypia to exclude existence of endometrial cancer in about 37 % in one study

Diagnostic hysteroscopy should be considered to facilitate or obtain an endometrial sample, especially where outpatient sampling fails or is nondiagnostic. ✓

Transvaginal ultrasound may have a role in diagnosing endometrial hyperplasia in pre- and postmenopausal women(>4mm). ✓

How Should Endometrial Hyperplasia Without Atypia be Managed?

What Should the Initial Management of Hyperplasia without Atypia be?

Women should be informed that the risk of endometrial hyperplasia 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.

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

What Should the Initial Management of Hyperplasia without Atypia be?

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.

Progestogen treatment is indicated in women who fail to regress following observation alone and in symptomatic women with abnormal uterine bleeding.

■ What Should the First-line Medical Treatment of Hyperplasia without Atypia be?

Both continuous oral and local intrauterine (levonorgestrel-releasing intrauterine system [LNG-IUS]) progestogens are effective in achieving regression of endometrial hyperplasia without atypia.80%

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 favourable bleeding profile and it is associated with fewer adverse effects.

LNG-IUS (levonrgestrel 52 mg release 20 microgram pe day)

What Should the First-line Medical Treatment of Hyperplasia without Atypia be?

Continuous progestogens should be used (medroxyprogesterone10–20 mg/day or norethisterone 10–15 mg/day) for women who decline the LNG-IUS. **B**

Cyclical progestogens should not be used because they are less effective in inducing regression of endometrial hyperplasia without atypia compared with continuous oral progestogens or the LNG-IUS. **A**

- **What Should the Duration of Treatment & Follow-up of Hyperplasia without Atypia be?**

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.

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.

What Should the Duration of Treatment & Follow-up of Hyperplasia without Atypia be?

Endometrial surveillance should be arranged at a minimum of 6-monthly intervals, although review schedules should be individualised and responsive to changes in a woman's clinical condition. At least two consecutive 6-monthly negative biopsies should be obtained prior to discharge.

D

In women at higher risk of relapse, such as women with a BMI of 35 or greater 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

Maintenance therapy — For women with complex EH without atypia, after regression to normal endometrium, maintenance progestin therapy may be required indefinitely if patients have risk factors for endometrial carcinoma (eg, obesity, diabetes, polycystic ovarian syndrome) or persistent postmenopausal bleeding.

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When is Surgical Management Appropriate for Women with Endometrial Hyperplasia without Atypia?

Hysterectomy should not be considered as a first-line treatment for hyperplasia without atypia because progestogen therapy induces histological and symptomatic remission in the majority of women and avoids the morbidity associated with major surgery.

C

Hysterectomy is indicated in women not wanting to preserve their fertility when (i) progression to atypical hyperplasia occurs during follow-up, or (ii) there is no histological regression of hyperplasia despite 12 months of treatment, or (iii) there is relapse of endometrial hyperplasia after completing progestogen treatment, or (iv) there is persistence of bleeding symptoms, or (v) the woman declines to undergo endometrial surveillance or comply with medical treatment.

C

When is Surgical Management Appropriate for Women with Endometrial Hyperplasia without Atypia?

Postmenopausal women requiring surgical management for endometrial hyperplasia without atypia should be offered a bilateral salpingooophorectomy together with the total hysterectomy. ✓

For premenopausal 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

Endometrial ablation is not recommended for the treatment of endometrial hyperplasia because complete and persistent endometrial destruction cannot be ensured and intrauterine adhesion formation may preclude future endometrial histological surveillance. D

How Should Atypical Hyperplasia be Managed?

What Should the Initial Management of Atypical Hyperplasia be?

Women with atypical hyperplasia should undergo a total hysterectomy because of the risk of underlying malignancy or progression to cancer.

What Should the Initial Management of Atypical Hyperplasia be?

Postmenopausal women with atypical hyperplasia should be offered bilateral salpingo-oophorectomy together with the total hysterectomy. ✓

For premenopausal 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

Endometrial ablation is not recommended because complete and persistent endometrial destruction cannot be ensured and intrauterine adhesion formation may preclude endometrial histological surveillance. C

- **How Should Women with Atypical Hyperplasia Who Wish to Preserve Their Fertility or Who are not Suitable for Surgery be Managed?**

First-line treatment with the LNG-IUS should be recommended (regression 90%), with oral progestogens as a second-best alternative (71%) **B**

To date, there have been no randomised trials comparing different regimens of hormonal treatments.
Megesterol acetate 80 mg po bid may increase to 160 mg po bid if no regressions
Or MPA 10 -20 MG PO daily not well studied
Or depot (MP) 150 mg every 3 months not well studied micronized progesterone (Vaginal) 200 mg daily not well studied
Combined estrogen/progestin contraceptives (pills, patches, rings) have not been studied for treatment of EH.

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

If persistent atypical EH is present at 6 to 12 months:

•The total progestin dose may be increased. An oral progestin may be given in combination with the LNg52/5 or the oral progestin dose may be increased.

•Endometrial sampling is then repeated in three months from inception of the additional therapy. If endometrium is normal, the patient may try to conceive a pregnancy. If the sample shows nonatypical EH, therapy may be continued, and repeat sampling can be done every 3 to 6 months until there is no EH. However, if there is persistent atypical EH or cancer at any time, the patient should have a hysterectomy.

Maintenance therapy — When endometrial sampling has demonstrated successful regression to a normal endometrium, the premenopausal patient may attempt to conceive a pregnancy in the near future, or if plans for pregnancy are not immediate, should be managed with progestin maintenance therapy. All postmenopausal women require maintenance therapy.

Non Progestin Medications in EH

- Gonadotropin-releasing hormone (GnRH) agonists were used in combination with a levonorgestrel-releasing intrauterine device.
- Aromatase inhibitors have been administered to block endogenous estrogen production in patients with EH.
- Ovulation induction with clomid or Aramatase inhibitor.
- Metformone has been shown to both have antiproliferative effects and to reduce insulin resistance, which may play a role in the development of endometrial carcinoma in overweight and obese females.
- Danazol has been used to successfully treat EH, but is seldom used due to significant side effects when taken orally

How Should Endometrial Hyperplasia be Managed In Women on Adjuvant Treatment for Breast Cancer?

What is the Risk of Developing Endometrial Hyperplasia 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.

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.

- **Should Women on Tamoxifen be Treated with Prophylactic Progestogen Therapy?**

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.

- **How Should Women Who Develop Endometrial Hyperplasia While on Tamoxifen Treatment for Breast Cancer be Managed?**

The need for tamoxifen should be reassessed and management should be according to the histological classification of endometrial hyperplasia and in conjunction with the woman's oncologist.

HRT and Endometrial Hyperplasia

■ Endometrial Hyperplasia and HRT

- Women with endometrial hyperplasia taking a sequential HRT preparation who wish to continue HRT should be advised to change to continuous progestogen intake using the LNG-IUS or a continuous combined HRT preparation.

- Women with endometrial hyperplasia taking a continuous combined preparation who wish to continue HRT should have their need to continue HRT reviewed. Discuss the limitations of the available evidence regarding the optimal progestogen regimen in this context. Consider using the LNG-IUS as a source of progestogen replacement.

How Should Endometrial Hyperplasia Confined to an Endometrial Polyp be Managed?

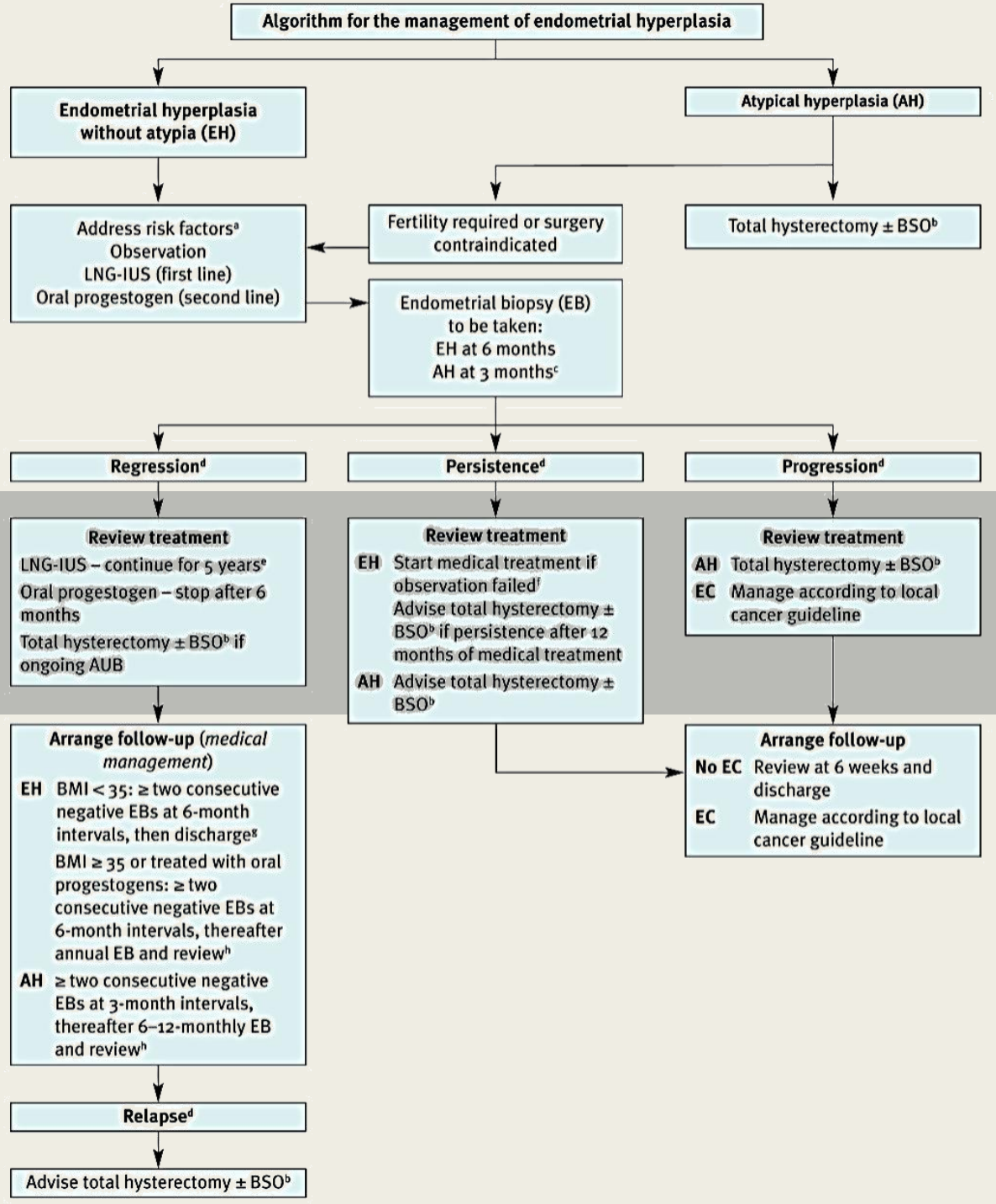
- **How Should Endometrial Hyperplasia Confined To**
- **An Endometrial Polyp Be Managed?**

Complete removal of the uterine polyp(s) is recommended and an endometrial biopsy should be obtained to sample the background endometrium.

In the absence of background endometrial hyperplasia, it seems reasonable to assume that removal of the polyp may be curative. There has been only a small quasi- randomised trial of 21 women, which compared use of the LNG-IUS with no treatment after removal of polyps with focal atypical hyperplasia. They found that after 5 years' follow-up there was no recurrence of atypia in either group.

Subsequent management should be according to the histological classification of endometrial hyperplasia.

Algorithm for the Management of Endometrial Hyperplasia

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