The Shrewsbury and Telford Hospital NHS Trust

ENDOMETRIAL HYPERPLASIA

Ref. 015

Version 2.2

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Comments	References to SaTH Guidelines in the text pertain to the latest version of the guideline on the intranet. Printed copies may not be the most up to date version.

For Triennial Review

Version	Date	History	Ratified By	Full Review Date
1	Sep 2016	New Guidance		Feb 2018
2	12 Feb 2018	Full Review	Gynae Governance	Feb 2021
2.1	8 Oct 2018	Reviewed with no changes. Review date extended	Gynae Governance	8th October 2021
2.2	November 2023	Reviewed with no changes. Review date extended	Dr Sahu	November 2026

1.0 Introduction and Background Epidemiology

Endometrial hyperplasia is defined as irregular proliferation of the endometrial glands with an increase in the gland to stroma ratio when compared with proliferative endometrium (1). It is the precursor to endometrial cancer and if left untreated can progress to cancer (2,4). In the UK, 8617 new cases of endometrial cancer were registered in 2012 (3). The incidence of endometrial hyperplasia is estimated to be at least three times higher than endometrial cancer (2,4) but there is less robust data regarding the incidence of endometrial hyperplasia. The overall incidence of endometrial hyperplasia in women aged between 18 and 90 has been estimated at 133/100,000 women (5).

1.1 Classification of Endometrial Hyperplasia

The 1994 WHO classification of endometrial hyperplasia was widely adopted and based upon both the complexity of the glandular architecture and the presence of nuclear atypia (1). It comprised four categories: (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(2).

The 2014 revised WHO classification (1) simply separates endometrial hyperplasia into two groups based upon the presence or absence of cytological atypia, i.e. (i) hyperplasia without atypia and (ii) atypical hyperplasia; the complexity of architecture is no longer part of the classification (24).

The diagnosis of EIN in the new WHO classification is considered interchangeable with atypical hyperplasia. This guideline has adopted the new 2014 WHO classification of endometrial hyperplasia, although much of the supporting evidence identified has used the 1994 WHO nomenclature categorising hyperplasia morphologically as simple or complex (24).

1.2 Risk of Progression

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.

The risk of developing endometrial cancer is highest in atypical hyperplasia. A case–control study nested in a cohort of 7947 women diagnosed with atypical hyperplasia found that the cumulative risk of cancer in 4 years was 8% (95% CI 1.31–14.6), which increased to 12.4% (95% CI 3.0–20.8) after 9 years and to 27.5% (95% CI 8.6–42.5) after 19 years (6). Atypical hyperplasia has also been associated with a rate of concomitant carcinoma of up to 43% in women undergoing hysterectomy (7).

2.0 Aim

The aim of this guideline is to provide clinicians with up-to-date evidence- based information regarding the management of endometrial hyperplasia.

3.0 Process

3.1 Clinical History

Review the patient's history, especially with regard to risk factors and pattern of bleeding.

Particular risk factors to establish in the history include:

- Obesity (often with diabetes and hypertension)
- Perimenopause or polycystic ovary syndrome (PCOS) associated with chronic anovulation
- Oestrogen-secreting ovarian tumours e.g. granulosa cell tumours
- Drug-induced endometrial stimulation e.g use of unopposed oestrogen replacement therapy at all doses in women with a uterus or long-term tamoxifen use
- Immunosuppression (8-14)

The most common presentation of endometrial hyperplasia is abnormal uterine bleeding. This includes heavy menstrual bleeding, inter-menstrual bleeding, irregular bleeding, unscheduled bleeding on hormone replacement therapy (HRT) and postmenopausal bleeding (2,3).

Review smear history, relevant past medical, surgical and gynaecological history.
Drug history should include review of use of HRT and Tamoxifen.

3.2 HRT and endometrial hyperplasia

In women with a uterus systemic oestrogen-only HRT should not be used. All women taking HRT should be encouraged to report any unscheduled vaginal bleeding promptly (24).

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 (24).

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 (24).

3.3 Women on adjuvant treatment for breast cancer

Women taking tamoxifen have increased risks of developing endometrial hyperplasia and cancer and they should be encouraged to report any abnormal vaginal bleeding or discharge promptly (24).

Aromatase inhibitors (Anastrozole, Exemestane and Letrozole) are not known to increase the risk of endometrial hyperplasia and cancer (24).

Although, the LNG-IUS prevents polyp formation and reduces the incidence of endometrial hyperplasia in women on Tamoxifen, its effect on breast cancer recurrence risk remains uncertain so its routine use cannot be recommended (24).

In women who develop endometrial hyperplasia while on Tamoxifen treatment for breast cancer, 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 (24).

3.4 Clinical Examination

Women presenting with abnormal vaginal bleeding where there may be endometrial hyperplasia should have: General examination to include abdomen and pelvis. Inspection of vulva, vagina and cervix using speculum examination and bimanual palpation.

3.5 Investigation

Diagnosis of endometrial hyperplasia requires histological examination of endometrial tissue either by outpatient endometrial biopsy (Pipelle biopsy) or other surgical endometrial sampling.

Transvaginal ultrasound scan (TVS) may have a role in diagnosing endometrial hyperplasia in pre and postmenopausal women. A TVS that detects an irregularity of the endometrial profile or an abnormal double layer endometrial thickness measurement would give further reason to perform an endometrial biopsy in women with postmenopausal bleeding (15,16). Systematic reviews have suggested a cut-off of ≥4 mm for ruling out endometrial cancer and have shown that the probability of cancer is reduced to less than 1% when the endometrial thickness is less than the cut-off (15, 17-19).

The role of ultrasound in premenopausal women is restricted to identifying structural abnormalities, as there seems to be an overlap between normal endometrial thickness and that caused by endometrial disease (21). However, for women with PCOS and absent withdrawal bleeds or abnormal uterine bleeding, a TVS should be considered, as advised by RCOG guidance (22).

Direct visualisation and biopsy of the uterine cavity using hysteroscopy should be undertaken where endometrial hyperplasia has been diagnosed within a polyp or other discrete focal lesion (24).

There is insufficient evidence evaluating CT or MRI or biomarkers as aids in the management of endometrial hyperplasia and their use is not routinely recommended (24).

3.6 Management

See below for pathway for management of endometrial hyperplasia without atypia and atypical endometrial hyperplasia

3.7 Endometrial hyperplasia confined to an endometrial polyp

Complete removal of the uterine polyp(s) is recommended and an endometrial biopsy should be obtained to sample the background endometrium (24).

Subsequent management should be according to the histological classification of endometrial hyperplasia (24).

3.8 Management of atypical hyperplasia

The risk of developing endometrial cancer is highest in atypical hyperplasia. A case–control study nested in a cohort of 7947 women diagnosed with atypical hyperplasia found that the cumulative risk of cancer in 4 years was 8% (95% CI 1.31–14.6), which increased to 12.4% (95% CI 3.0–20.8) after 9 years and to 27.5% (95% CI 8.6–42.5) after 19 years (6). Atypical hyperplasia has also been associated with a rate of concomitant carcinoma of up to 43% in women undergoing hysterectomy (7).

Due to the risks of disseminating malignancy, morcellation of the uterus should be avoided. Supracervical hysterectomy should not be performed (25).

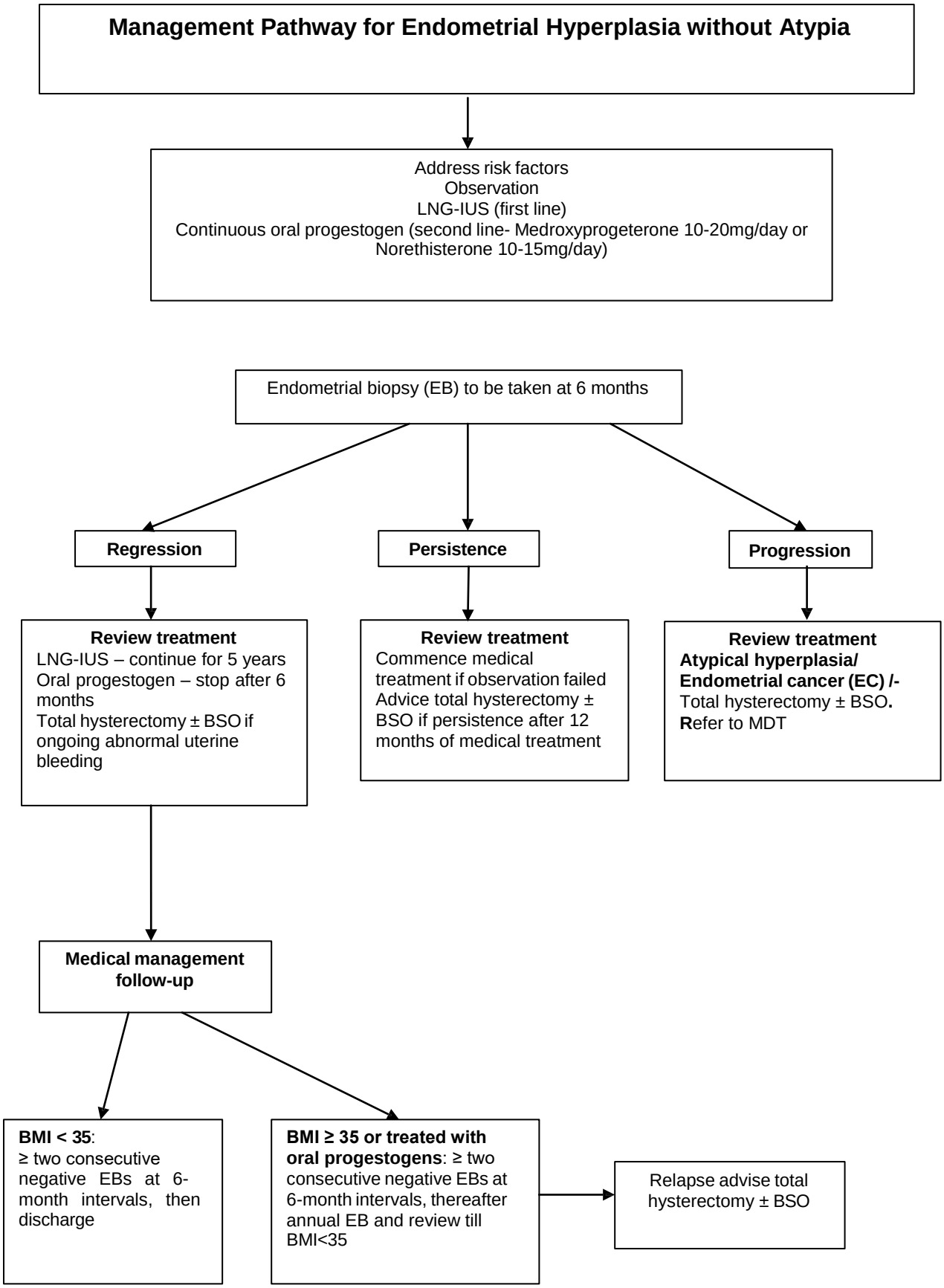
Due to the risk of underlying malignancy, bilateral salpingo-oophorectomy should be performed in all peri- and postmenopausal women undergoing hysterectomy for atypical hyperplasia (26)

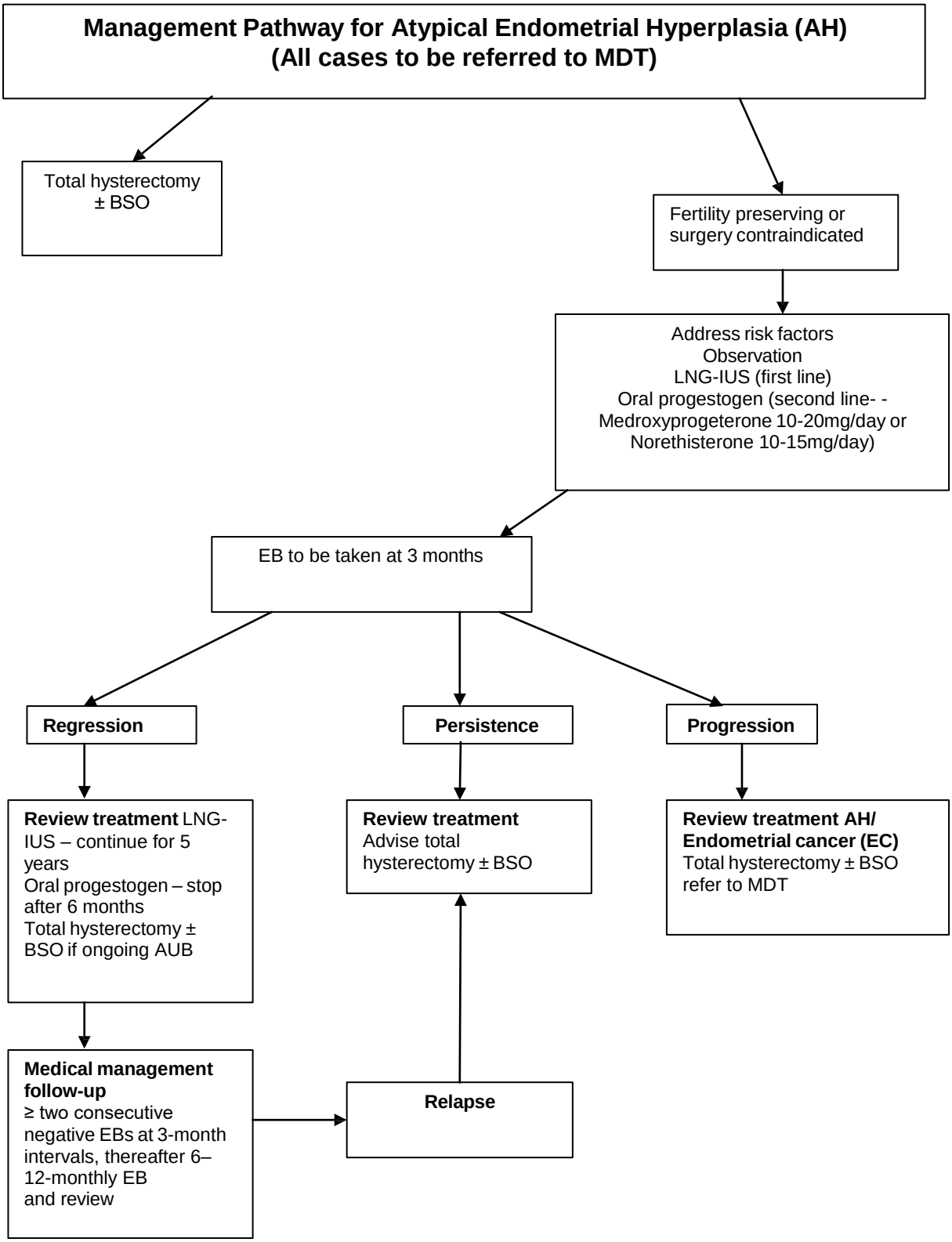
Use of the Mirena IUS

The Mirena IUS is not licensed for use as part of the management and treatment of Endometrial Hyperplasia both with and without atypia. It is however a recommended treatment in this local guideline and in national guidelines such as the RCOG's Green Top Guideline.

As its use is unlicensed, this needs to be explained to the patient and an appropriate management plan for follow up is indicated, such as when it needs removing and by whom. You also need to arrange appropriate follow such as repeat Pipelle biopsies (see endometrial hyperplasia management flow charts below).

Good practice is only to insert the Mirena IUS when you have the histology report confirming the abnormality and not before.


Management Pathway for Endometrial Hyperplasia without Atypia
Address risk factors
Observation
LNG-IUS (first line)
Continuous oral progestogen (second line- Medroxyprogeterone 10-20mg/day or Norethisterone 10-15mg/day)
Endometrial biopsy (EB) to be taken at 6 months
Regression
Persistence
Progression
Review treatment
LNG-IUS – continue for 5 years
Oral progestogen – stop after 6 months
Total hysterectomy ± BSO if ongoing abnormal uterine bleeding
Review treatment
Commence medical treatment if observation failed
Advice total hysterectomy ± BSO if persistence after 12 months of medical treatment
Review treatment
Atypical hyperplasia/ Endometrial cancer (EC) /-
Total hysterectomy ± BSO.
Refer to MDT
Medical management follow-up
BMI < 35:
≥ two consecutive negative EBs at 6-month intervals, then discharge
BMI ≥ 35 or treated with oral progestogens: ≥ two consecutive negative EBs at 6-month intervals, thereafter annual EB and review till BMI<35
Relapse advise total hysterectomy ± BSO


Management Pathway for Atypical Endometrial Hyperplasia (AH)
(All cases to be referred to MDT)
Total hysterectomy
± BSO
Fertility preserving or
surgery contraindicated
Address risk factors
Observation
LNG-IUS (first line)
Oral progestogen (second line- -
Medroxyprogeterone 10-20mg/day or
Norethisterone 10-15mg/day)
EB to be taken at 3 months
Regression
Persistence
Progression
Review treatment LNG-IUS – continue for 5 years
Oral progestogen – stop after 6 months
Total hysterectomy ± BSO if ongoing AUB
Review treatment
Advise total hysterectomy ± BSO
Review treatment AH/ Endometrial cancer (EC)
Total hysterectomy ± BSO
refer to MDT
Medical management follow-up
≥ two consecutive negative EBs at 3-month intervals, thereafter 6–12-monthly EB
and review
Relapse

4.0 Training

4.1 All staff should receive regular updates regarding new guidelines

4.2 All staff should be familiar with RCOG guidance

5.0 Auditable topics

- 100% of women with endometrial hyperplasia with a BMI greater than 30 should be advised to lose weight
- 100% of women with endometrial hyperplasia without atypia should have at least two negative endometrial biopsies prior to discharge
- 100% of postmenopausal women with atypical hyperplasia should undergo a total hysterectomy and bilateral salpingo-oophorectomy if not medically contraindicated

6.0 Useful resources and support groups

- Cancer Research UK. *Endometrial hyperplasia* [http://www.cancerresearchuk.org/about-cancer/cancers-in- general/cancer-questions/endometrial-hyperplasia]
- Patient. *Endometrial Hyperplasia* [http://patient.info/doctor/endometrial- hyperplasia]
- Shrewsbury and Telford NHS Trust patient information leaflet

References

1. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. *WHO Classification of Tumours of Female Repro ductive Organs*. 4th ed. [Lyon]: IARC; 2014.
2. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer* 1985;56:403–12.
3. Cancer Research UK. Uterine cancer incidence statistics. Uterine cancer incidence by UK region [http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence#heading-Zero]. Accessed 2015 Nov 25.
4. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, et al. Incidence of endometrial hyperplasia. *Am J Obstet Gynecol* 2009;200:678.e1–6.
5. http://blog.utp.edu.co/maternoinfantil/files/2012/04/hiperplasia-endometrial.pdf
6. Lacey JV Jr, Sherman ME, Rush BB, Ronnett BM, Ioffe OB, Duggan MA, et al. Absolute risk of endometrial carcinoma during 20-year follow-up among women with endometrial hyperplasia. *J Clin Oncol* 2010;28:788–92.
7. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ 2nd, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer* 2006;106:812–9.
8. Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. *Am J Obstet Gynecol* 1999;181:525–9.
9. Ricci E, Moroni S, Parazzini F, Surace M, Benzi G, Salerio B, et al. Risk factors for endometrial hyperplasia: results from a case-control study. *Int J Gynecol Cancer* 2002;12: 257–60.
10 Epplein M, Reed SD, Voigt LF, Newton KM, Holt VL, Weiss NS. Risk of complex and atypical endometrial hyperplasia in relation to anthropometric measures and reproductive history. *Am J Epidemiol* 2008;168:563–70.
11. Viola AS, Gouveia D, Andrade L, Aldrighi JM, Viola CF, Bahamondes L. Prevalence of endometrial cancer and hyperplasia in non-symptomatic overweight and obese women. *Aust N Z J Obstet Gynaecol* 2008;48:207–13.
12. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev* 2012;(8):CD000402.
13. Bobrowska K, Kami´nski P, Cyganek A, Pietrzak B, Jabiry-Zieniewicz Z, Durlik M, et al. High rate of endometrial hyperplasia in renal transplanted women. *Transplant Proc* 2006;38:177–9.
14. Gallos ID, Alazzam M, Clark TJ, Faraj R, Rosenthal AN, Smith PP, Gupta JK. Management of endometrial hyperplasia. Green-top Guideline No. 67 RCOG/BSGE Joint Guideline. 2016.
15. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. *Obstet Gynecol* 2010;116:160–7
16. Scottish Intercollegiate Guidelines Network (SIGN). *Investigation of post-menopausal bleeding*. SIGN publication no. 61. Edinburgh: SIGN; 2002.
17. Tabor A, Watt HC, Wald NJ. Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. *Obstet Gynecol* 2002;99:663–70
18. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. *Acta Obstet Gynecol Scand* 2002;81:799–816.
19. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *JAMA* 1998;280:1510–7.
20. Wolfman W, Leyland N, Heywood M, Singh SS, Rittenberg DA, Soucy R, et al.; Society of Obstetricians and Gynaecologists of Canada. Asymptomatic endometrial thickening. *J Obstet Gynaecol Can* 2010;32:990–9.
21. Getpook C, Wattanakumtornkul S. Endometrial thickness screening in premenopausal women with abnormal uterine bleeding. *J Obstet Gynaecol Res* 2006;32:588–92.
22. Royal College of Obstetricians and Gynaecologists. *Long-term Consequences of Polycystic Ovary Syndrome*. Green-top Guideline No. 33. London: RCOG; 2014.
23. Cheung AP. Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome. *Obstet Gynecol* 2001;98:325–31
24. RCOG/BSGE Green-top Guideline No 67 Management of endometrial hyperplasia.
25. American College of Obstetricians and Gynaecologists. Supracervical hysterectomy. ACOG Committee Opinion No. 388. Obstet Gynecol 2007; 110:2015-7.
26. Parker WH, Feskanich D, Broder MS, Chang E, Shoupe D, Farquhar CM, et al. Long-term mortality associated with oophorectomy comparted with ovarian conservation in the nurses' health study. Obstet Gynecol 2013;121:709-16.