- 35. Allen NE, Tsilidis KK, Key TJ, Dossus L, Kaaks R, Lund E, et al. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. Am J Epidemiol. 2010;172(12):1394-403.
- 36. Langer RD, Landgren BM, Rymer J, Helmond FA. Effects of tibolone and continuous combined conjugated equine estrogen/medroxyprogesterone acetate on the endometrium and vaginal bleeding: results of the OPAL study. Am J Obstet Gynecol. 2006;195(5):1320-7.
- 37. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. Jama. 1995;273(3):199-208.
- 38. Harman SM, Black DM, Naftolin F, Brinton EA, Budoff MJ, Cedars MI, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Ann Intern Med. 2014;161(4):249-60.
- 39. Fournier A, Dossus L, Mesrine S, Vilier A, Boutron-Ruault MC, Clavel-Chapelon F, et al. Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008. Am J Epidemiol. 2014;180(5):508-17.
- 40. Birkhäuser MH, Panay N, Archer DF, Barlow D, Burger H, Gambacciani M, et al. Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. Climacteric. 2008;11(2):108-23.
- 41. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, et al. Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. N Engl J Med. 2016;374(13):1221-31.
- 42. Hipolito Rodrigues MA, Gompel A. Micronized progesterone, progestins, and menopause hormone therapy. Women Health. 2021;61(1):3-14.
- 43. Sriprasert I, Mert M, Mack WJ, Hodis HN, Shoupe D. Use of oral estradiol plus vaginal progesterone in healthy postmenopausal women. Maturitas. 2021;154:13-9.
- 44. Abdullahi Idle S, Hamoda H. Outcomes of endometrial assessment in women with unscheduled bleeding on hormone replacement therapy. Post Reprod Health. 2019;25(2):95-9.
- 45. Feeley KM, Wells M. Hormone replacement therapy and the endometrium. J Clin Pathol. 2001;54(6):435-40.
- 46. Levine D, Gosink BB, Johnson LA. Change in endometrial thickness in postmenopausal women undergoing hormone replacement therapy. Radiology. 1995;197(3):603-8.
- 47. Sturdee DW, Ulrich LG, Barlow DH, Wells M, Campbell MJ, Vessey MP, et al. The endometrial response to sequential and continuous combined oestrogen-progestogen replacement therapy. Bjog. 2000;107(11):1392-400.
- 48. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018;178(9):1210-22.
- 49. Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. Br J Obstet Gynaecol. 1995;102(2):133-6.
- 50. van Hanegem N, Breijer MC, Slockers SA, Zafarmand MH, Geomini P, Catshoek R, et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. Bjog. 2017;124(2):231-40.

- Mattsson L, Ipsen HE, Granqvist CJ, Kokot-Kierepa M. Ultra-low-dose estradiol and norethisterone acetate: bleeding patterns and other outcomes over 52 weeks of therapy. Climacteric. 2015;18(3):419-25.
- 52. Habiba MA, Bell SC, Abrams K, al-Azzawi F. Endometrial responses to hormone replacement therapy: the bleeding pattern. Hum Reprod. 1996;11(3):503-8.
- 53. Thorneycroft IH, Gibbons WE. Vaginal bleeding patterns in women receiving hormone replacement therapy. Impact of various progestogen regimens. J Reprod Med. 1999;44(2 Suppl):209-14.
- 54. Ylikorkala O, Rozenberg S. Efficacy and tolerability of fully transdermal hormone replacement in sequential or continuous therapy at two doses of progestogen in postmenopausal women. Maturitas. 2000;37(2):83-93.
- 55. NICE. National Institute for Health and Clinical Excellence Guideline. Suspected Cancer: Recognition and Referral NG122023 21st November 2023. Available from: https://www.nice.org.uk/guidance/ng12.
- 56. Ferrazzi E, Torri V, Trio D, Zannoni E, Filiberto S, Dordoni D. Sonographic endometrial thickness: a useful test to predict atrophy in patients with postmenopausal bleeding. An Italian multicenter study. Ultrasound Obstet Gynecol. 1996;7(5):315-21.
- 57. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. Am J Obstet Gynecol. 2003;188(2):401-8.
- 58. 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(9):799-816.
- 59. 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(1):160-7.
- 60. Wong AS, Lao TT, Cheung CW, Yeung SW, Fan HL, Ng PS, et al. Reappraisal of endometrial thickness for the detection of endometrial cancer in postmenopausal bleeding: a retrospective cohort study. Bjog. 2016;123(3):439-46.
- 61. Timmermans A, Opmeer BC, Veersema S, Mol BW. Patients' preferences in the evaluation of postmenopausal bleeding. Bjog. 2007;114(9):1146-9.
- 62. Fung LWY, Cheung ECW, Wong ASW, Sahota DS, Lao TTH. Patient acceptance of transvaginal sonographic endometrial thickness assessment compared with hysteroscopy and biopsy for exclusion of endometrial cancer in cases of postmenopausal bleeding. Hong Kong Med J. 2022;28(2):133-9.
- 63. Doll KM, Romano SS, Marsh EE, Robinson WR. Estimated Performance of Transvaginal Ultrasonography for Evaluation of Postmenopausal Bleeding in a Simulated Cohort of Black and White Women in the US. JAMA Oncol. 2021;7(8):1158-65.
- 64. Clark TJ, Barton PM, Coomarasamy A, Gupta JK, Khan KS. Investigating postmenopausal bleeding for endometrial cancer: cost-effectiveness of initial diagnostic strategies. Bjog. 2006;113(5):502-10.
- 65. Cooper NA, Barton PM, Breijer M, Caffrey O, Opmeer BC, Timmermans A, et al. Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis. Health Technol Assess. 2014;18(24):1-201, v-vi.

- 66. Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2022;270:50-89.
- 67. Van den Bosch T, Van Schoubroeck D, Domali E, Vergote I, Moerman P, Amant F, et al. A thin and regular endometrium on ultrasound is very unlikely in patients with endometrial malignancy. Ultrasound Obstet Gynecol. 2007;29(6):674-9.
- 68. Affinito P, Palomba S, Pellicano M, Sorrentino C, Di Carlo C, Morgera R, et al. Ultrasonographic measurement of endometrial thickness during hormonal replacement therapy in postmenopausal women. Ultrasound Obstet Gynecol. 1998;11(5):343-6.
- 69. Langer RD, Pierce JJ, O'Hanlan KA, Johnson SR, Espeland MA, Trabal JF, et al. Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease. Postmenopausal Estrogen/Progestin Interventions Trial. N Engl J Med. 1997;337(25):1792-8.
- 70. Li Z, Li L. The incidence and predictors of gynecologic malignancies among postmenopausal patients with endometrial fluid collection. Arch Gynecol Obstet. 2019;299(4):1071-6.
- 71. Breijer MC, Peeters JA, Opmeer BC, Clark TJ, Verheijen RH, Mol BW, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2012;40(6):621-9.
- 72. Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol. 2011;12(1):38-48.
- 73. Vitale SG, Riemma G, Haimovich S, Carugno J, Alonso Pacheco L, Perez-Medina T, et al. Risk of endometrial cancer in asymptomatic postmenopausal women in relation to ultrasonographic endometrial thickness: systematic review and diagnostic test accuracy meta-analysis. Am J Obstet Gynecol. 2023;228(1):22-35.e2.
- 74. Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol. 2004;24(5):558-65.
- 75. Ghoubara A, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women determining an optimum threshold for prediction of atypical hyperplasia and cancer. J Obstet Gynaecol. 2018;38(8):1146-9.
- 76. Clark TJ. Hysteroscopy is needed in the diagnostic workup of postmenopausal bleeding. Bjog. 2017;124(2):241.
- 77. EMA. Committee for Medicinal Products for Human Use European Medicines Agency: Guideline on the clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women. EMEA/CHMP/021/972005 21st November 2023. Available from: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-hormone-replacement-therapy-oestrogen-deficiency-symptoms.
- 78. SIGN. Scottish Intercollegiate Guidelines Network: Investigation of postmenopausal bleeding: a national clinical guideline2002 21st November 2023. Available from: Investigation of post-menopausal bleeding (sign.ac.uk).
- 79. RCOG. Royal College of Obstetricians and Gynaecologists: Management of Endometrial Hyperplasia Greentop Guideline No 672016 21st November 2023. Available from: https://www.rcog.org.uk/media/knmjbj5c/gtg_67_endometrial_hyperplasia.pdf.

- 80. Suhonen SP, Allonen HO, Lähteenmäki P. Sustained-release estradiol implants and a levonorgestrel-releasing intrauterine device in hormone replacement therapy. Am J Obstet Gynecol. 1995;172(2 Pt 1):562-7.
- 81. Antoniou G, Kalogirou D, Karakitsos P, Antoniou D, Kalogirou O, Giannikos L. Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints versus estradiol-releasing vaginal ring with a vaginal progesterone suppository: clinical and endometrial responses. Maturitas. 1997;26(2):103-11.
- 82. Depypere HT, Hillard T, Erkkola R, Lukkari-Lax E, Kunz M, Rautiainen P, et al. A 60-month non-comparative study on bleeding profiles with the levonorgestrel intrauterine system from the late transition period to estrogen supplemented menopause. Eur J Obstet Gynecol Reprod Biol. 2010;153(2):176-80.
- 83. Raudaskoski TH, Lahti El, Kauppila AJ, Apaja-Sarkkinen MA, Laatikainen TJ. Transdermal estrogen with a levonorgestrel-releasing intrauterine device for climacteric complaints: clinical and endometrial responses. Am J Obstet Gynecol. 1995;172(1 Pt 1):114-9.
- 84. Suvanto-Luukkonen E, Sundström H, Penttinen J, Läärä E, Pramila S, Kauppila A. Percutaneous estradiol gel with an intrauterine levonorgestrel releasing device or natural progesterone in hormone replacement therapy. Maturitas. 1997;26(3):211-7.
- 85. Suvanto-Luukkonen E, Malinen H, Sundström H, Penttinen J, Kauppila A. Endometrial morphology during hormone replacement therapy with estradiol gel combined to levonorgestrel-releasing intrauterine device or natural progesterone. Acta Obstet Gynecol Scand. 1998;77(7):758-63.
- 86. Raudaskoski T, Tapanainen J, Tomás E, Luotola H, Pekonen F, Ronni-Sivula H, et al. Intrauterine 10 microg and 20 microg levonorgestrel systems in postmenopausal women receiving oral oestrogen replacement therapy: clinical, endometrial and metabolic response. Bjog. 2002;109(2):136-44.
- 87. Archer DF, Hendrix S, Gallagher JC, Rymer J, Skouby S, Ferenczy A, et al. Endometrial effects of tibolone. J Clin Endocrinol Metab. 2007;92(3):911-8.
- 88. Di Carlo C, Sammartino A, Di Spiezio Sardo A, Tommaselli GA, Guida M, Mandato VD, et al. Bleeding patterns during continuous estradiol with different sequential progestogens therapy. Menopause. 2005;12(5):520-5.
- 89. Darj E, Nilsson S, Axelsson O, Hellberg D. Clinical and endometrial effects of oestradiol and progesterone in post-menopausal women. Maturitas. 1991;13(2):109-15.
- 90. Gillet JY, Andre G, Faguer B, Erny R, Buvat-Herbaut M, Domin MA, et al. Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study. Maturitas. 1994;19(2):103-15.
- 91. Pélissier C, Maroni M, Yaneva H, Brin S, Peltier-Pujol F, Jondet M. Chlormadinone acetate versus micronized progesterone in the sequential combined hormone replacement therapy of the menopause. Maturitas. 2001;40(1):85-94.
- 92. Dupont A, Dupont P, Cusan L, Tremblay M, Rioux J, Cloutier D, et al. Comparative endocrinological and clinical effects of percutaneous estradiol and oral conjugated estrogens as replacement therapy in menopausal women. Maturitas. 1991;13(4):297-311.
- 93. Pickar JH, Archer DF, Goldstein SR, Kagan R, Bernick B, Mirkin S. Uterine bleeding with hormone therapies in menopausal women: a systematic review. Climacteric. 2020;23(6):550-8.

- 94. von Holst T, Lang E, Winkler U, Keil D. Bleeding patterns in peri and postmenopausal women taking a continuous combined regimen of estradiol with norethisterone acetate or a conventional sequential regimen of conjugated equine estrogens with medrogestone. Maturitas. 2002;43(4):265-75.
- 95. Rouskova D, Mittmann K, Schumacher U, Dietrich H, Zimmermann T. Effectiveness, tolerability and acceptance of an oral estradiol/levonorgestrel formulation for the treatment of menopausal complaints: a non-interventional observational study over six cycles of 28 days. Gynecol Endocrinol. 2014;30(10):712-6.
- 96. Lou YY, Kannappar J, Sathiyathasan S. Unscheduled bleeding on HRT do we always need to investigate for endometrial pathology? International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2017;6(10):4174-8.
- 97. Hillard T. Management of bleeding problems with hormone replacement therapy. J Fam Plann Reprod Health Care. 2002;28(4):182-4.
- 98. Hillard T, Lunsden LM, Rees M. Bleeding on sequential HRT and endometrial thickness predict success of transition from sequential hormone replacement therapy to continuous combined transdermal hormone replacement therapy. J Br Menopause Soc 2001;7:18-9.

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