

Abnormal Uterine Bleeding in Premenopausal Women: Indications for Endometrial Sampling

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MICHIGAN MEDICINE

FRIDAY, DECEMBER 1, 2019



DISCLOSURES

- None



OBJECTIVES

- Identify risk factors for the development of endometrial hyperplasia and malignancy
- Outline the endometrial biopsy procedure
- Review the benefits, risks, limitations, and alternatives to an endometrial biopsy

SURVEY





What is your medical specialty?

Family Medicine

Internal Medicine

Obstetrics/Gynecology

Other specialty



What is your role?

Attending physician

Advanced Practice Provider

Resident

Medical Student

Other

How often do you perform an office endometrial biopsy?

Never

Once a month

Less than 4 times a
month

At least 4 times a month

ABNORMAL UTERINE BLEEDING



ABNORMAL UTERINE BLEEDING

- Encompasses menstrual bleeding of abnormal
 - Quantity
 - Duration
 - Schedule
- A United States population-based survey of women ages 18 to 50 years reported an annual prevalence rate of 53 per 1000 women
- Impacts quality of life, productivity, and healthcare services

ABNORMAL UTERINE BLEEDING

- P** - Polyp
 - A** - Adenomyosis
 - L** - Leiomyoma
 - M** - Malignancy & Hyperplasia
-

STRUCTURAL

- C** - Coagulopathy
- O** - Ovulatory Dysfunction
- E** - Endometrial
- I** - Iatrogenic
- N** - Not yet classified

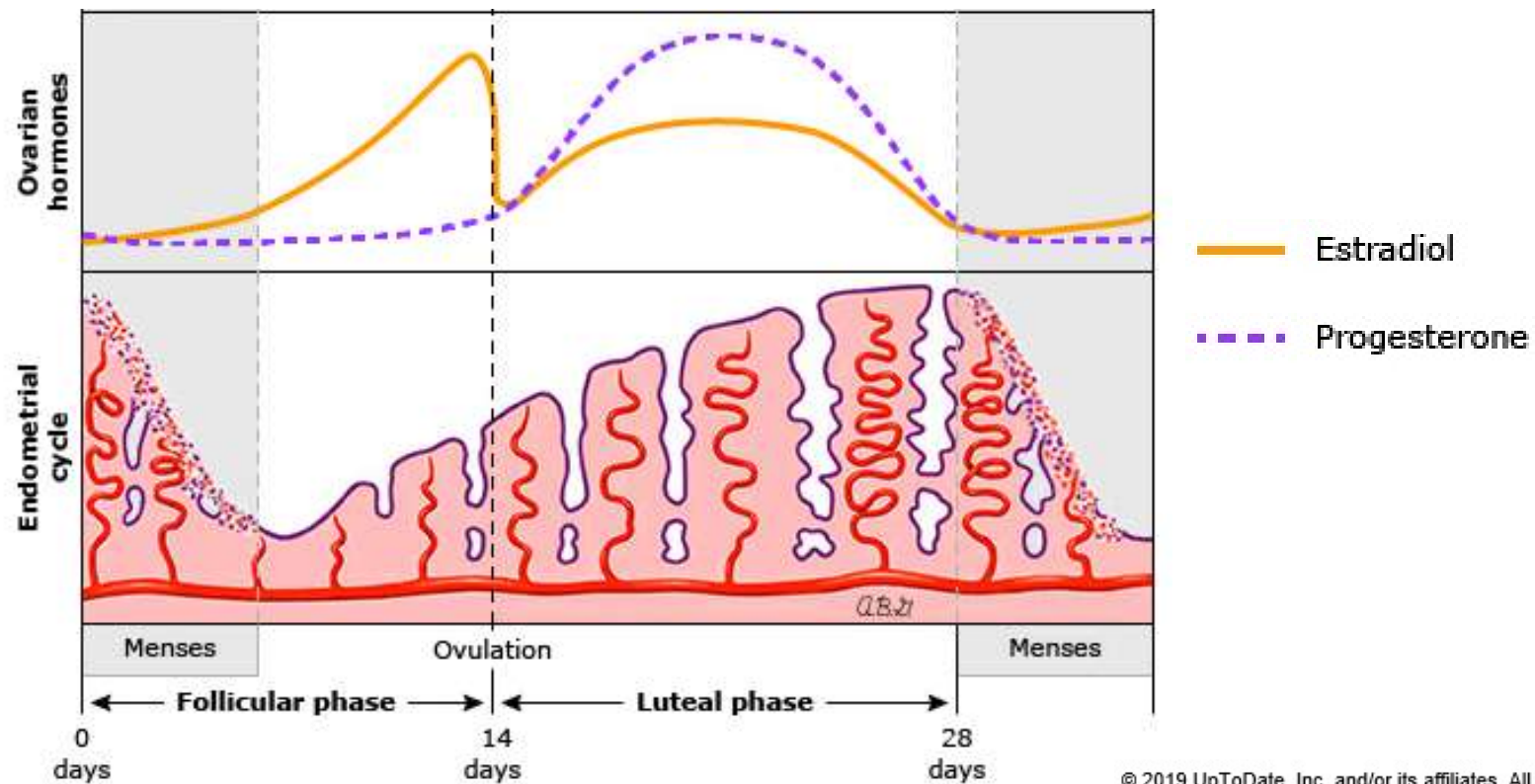
NON- STRUCTURAL

EVALUATION WITH AN ENDOMETRIAL BIOPSY (EMB)

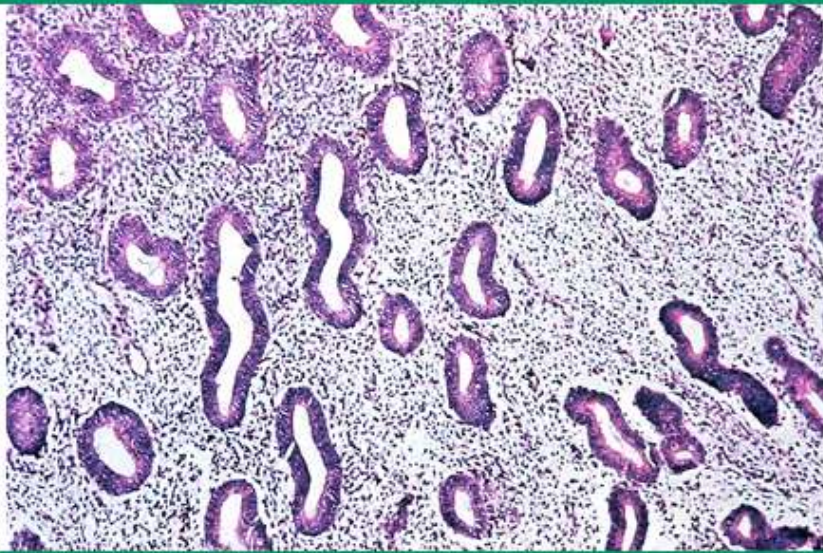


EMB: PURPOSE

- To determine the status of the endometrium in the menstrual cycle



Proliferative endometrium

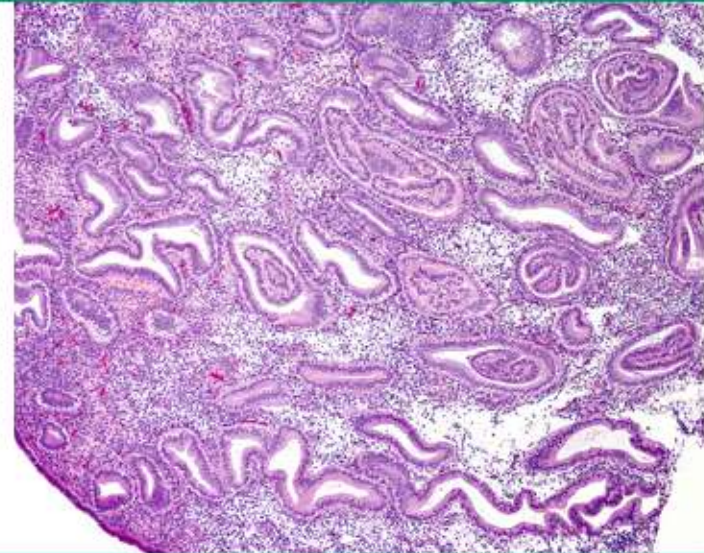


Note the straight non-convoluted glands, without glandular crowding.

Courtesy of Russell S Vang, MD.

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Secretory endometrium



Note tortuous glands, subnuclear vacuoles, without glandular crowding.

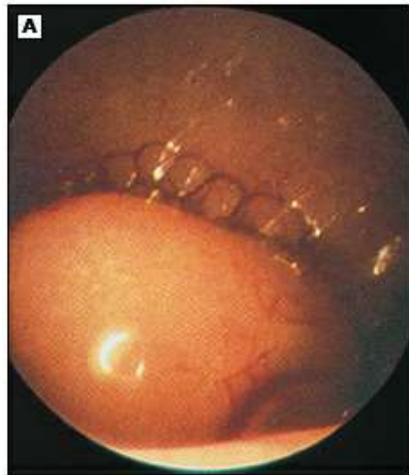
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EMB: PURPOSE

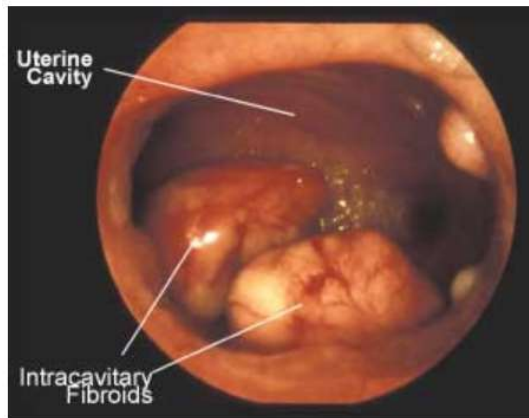
- To evaluate for endometrial pathology

POLYPS



Baggish

LEIOMYOMAS

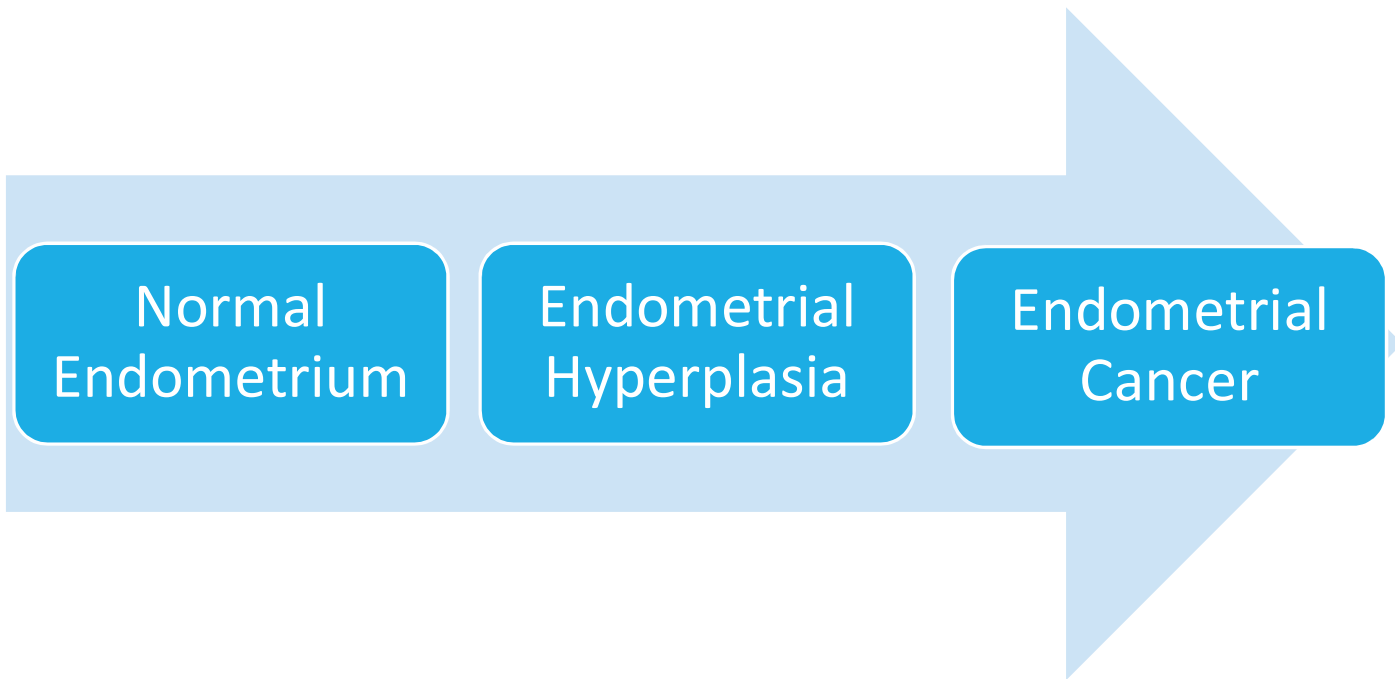


Indman

MALIGNANCY



hysteroscopynewsletter.com



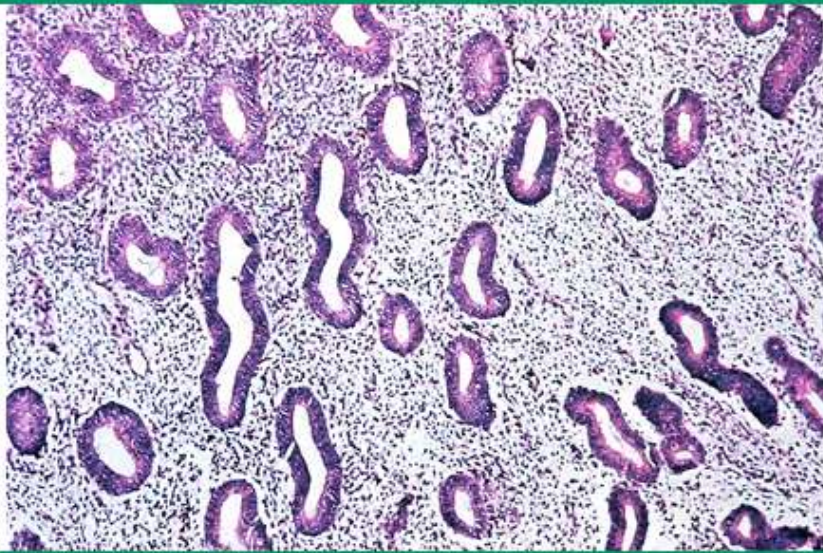
Normal
Endometrium

Endometrial
Hyperplasia

Endometrial
Cancer



Proliferative endometrium

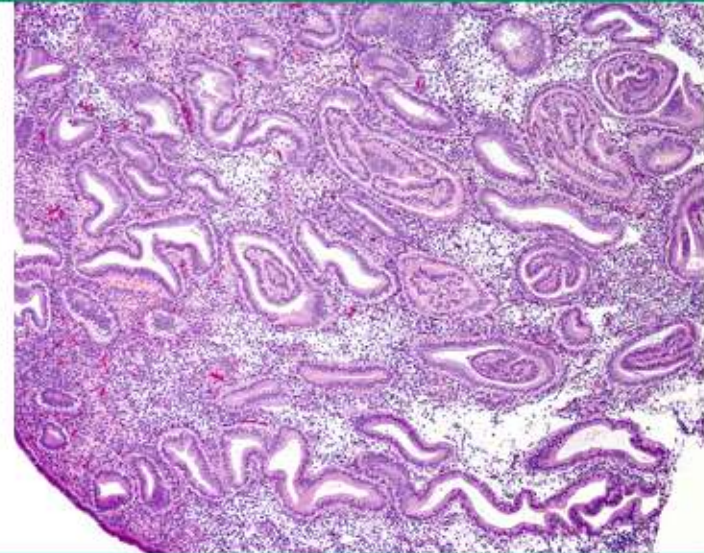


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Secretory endometrium

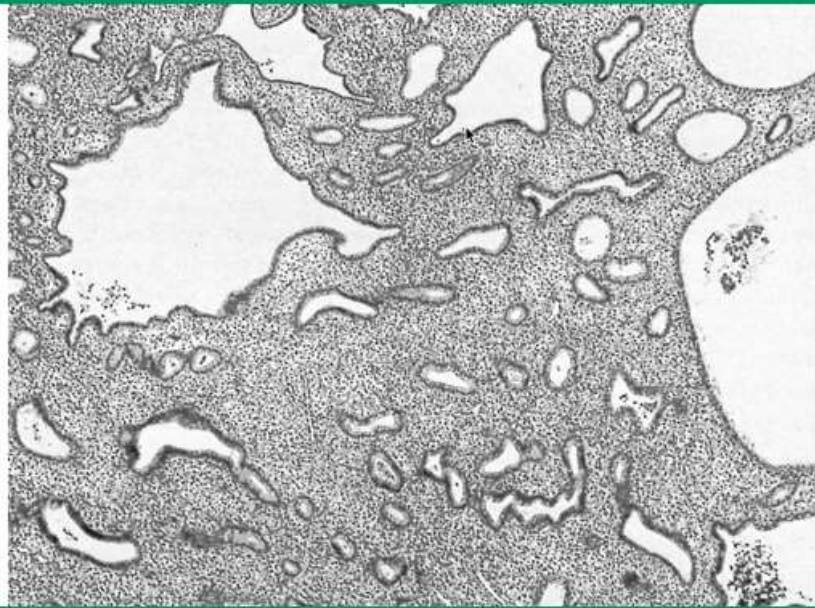


Note tortuous glands, subnuclear vacuoles, without glandular crowding.

Courtesy of Russell S Vang, MD.

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Simple endometrial hyperplasia

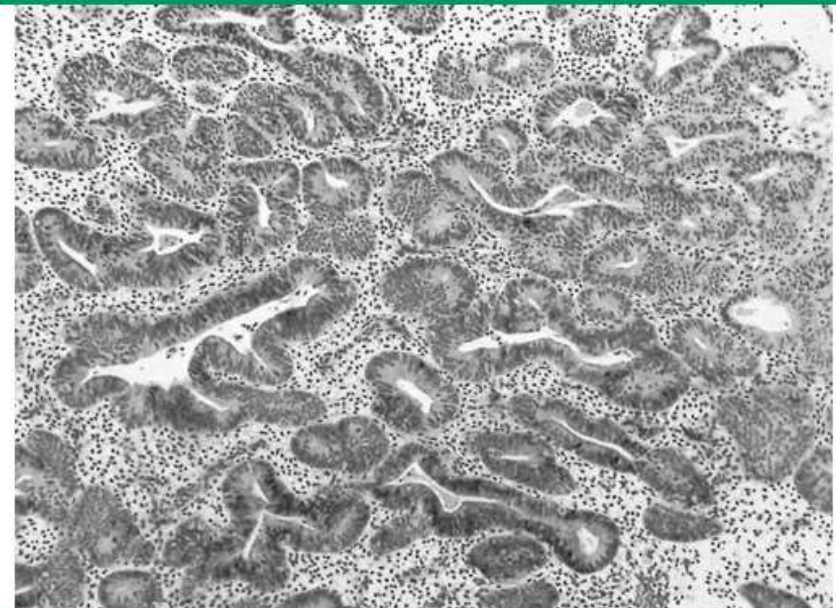


The endometrial glands in this lesion are irregularly distributed but widely separated by stroma, which is also hyperplastic. The glands are mostly round or tubular, with only a few angularities encountered.

Reproduced with permission from: Silverberg SG, Kurman RJ. Tumors of the Uterine Corpus and Gestational Trophoblastic Disease. AFIP Atlas of Tumor Pathology, version 2.0, American Registry of Pathology, Washington DC 1995.

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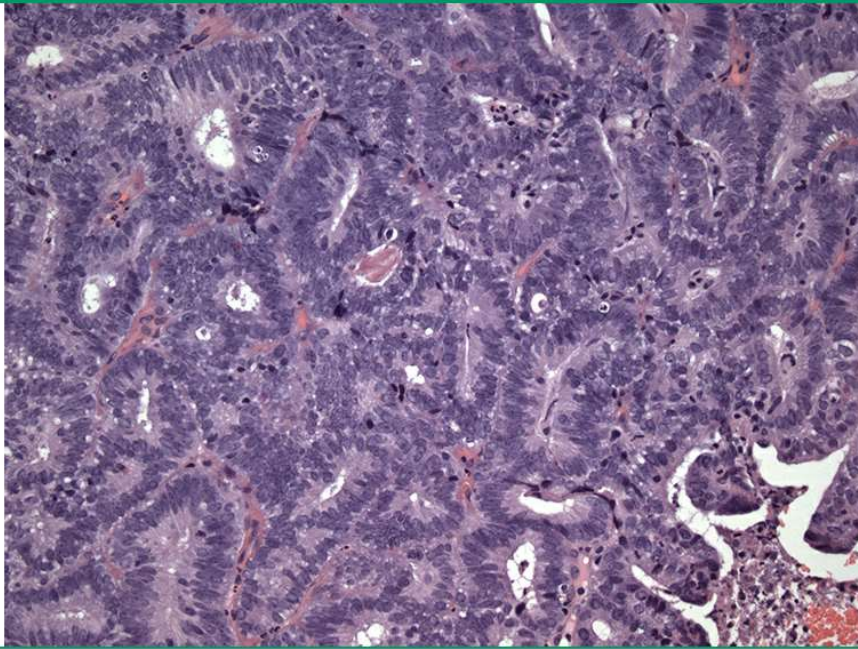
Complex endometrial hyperplasia



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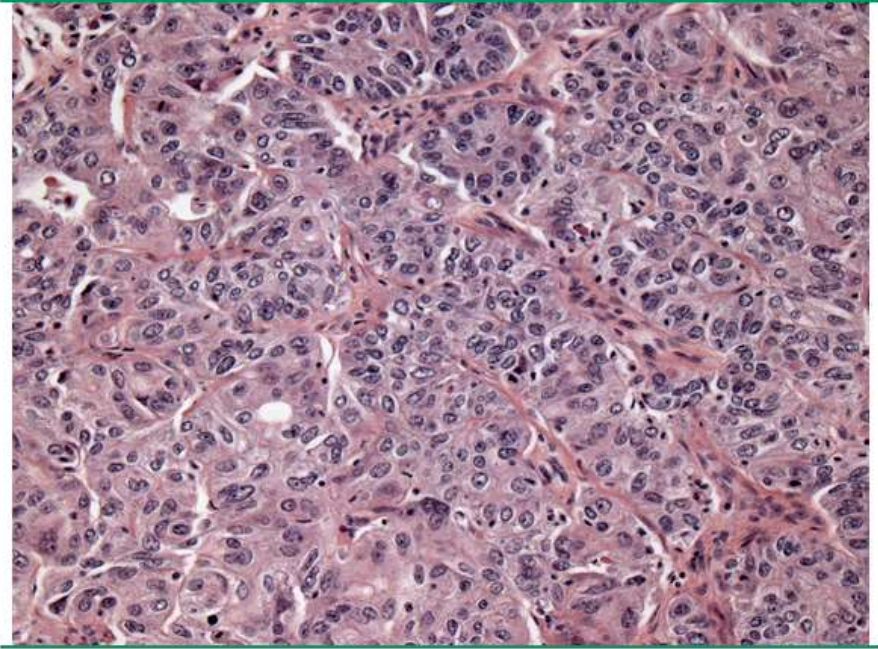
Endometrioid endometrial carcinoma, grade 1



Courtesy of Margaret M Steinhoff, MD.

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Endometrioid endometrial carcinoma, grade 3

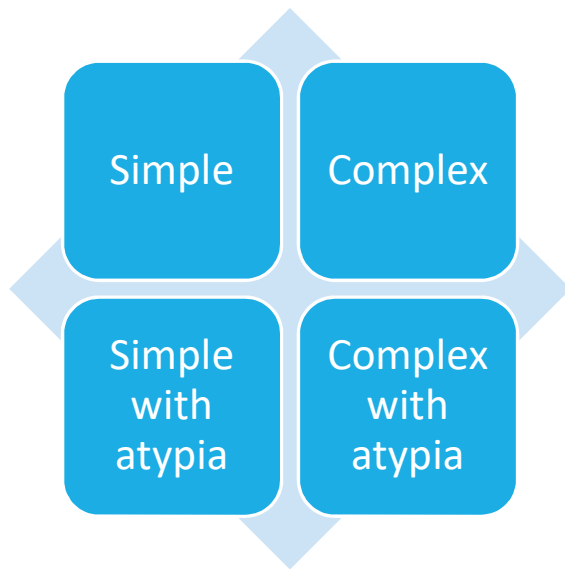


Courtesy of Margaret M Steinhoff, MD.

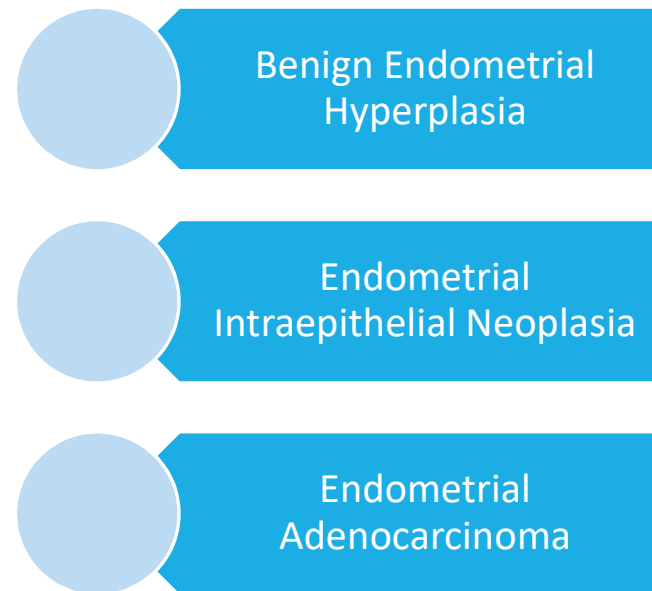
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ENDOMETRIAL HYPERPLASIA

WHO94 SCHEMA



ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA DIAGNOSTIC SCHEMA



ENDOMETRIAL CANCER

- Endometrial cancer is the most commonly diagnosed gynecologic malignancy in the United States
- The American Cancer Society estimates that in 2019
 - 61,880 new cases will be diagnosed
 - 12,160 women will die from cancers of the uterine body
 - These estimates include both endometrial and uterine sarcomas
- Classification
 - Type I: Endometrioid
 - Type II: Non-endometrioid (papillary serous and clear cell)

RISK FACTORS



RISK FACTORS

- Nulliparity
- Early menarche
- Late menopause
- History of Infertility
- Obesity (BMI >30)
- Chronic anovulation/Menstrual irregularities
- Older age
- History of T2DM, Hypertension, gallbladder disease, or thyroid disease

RISK FACTORS

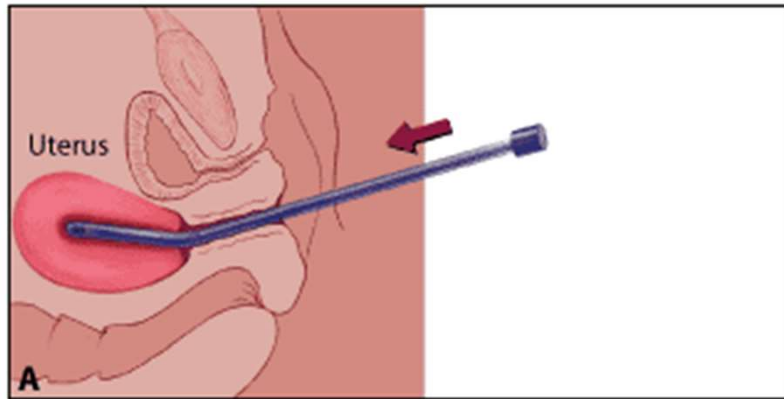
- Residency in North America or Northern Europe
- Higher level of education or income
- White race
- Unopposed estrogen
- Tamoxifen use
- Estrogen-producing tumor
- Failed Medical Management
- Lynch Syndrome/Cowden disease

Table 1. Risk Factors for Type I Uterine Corpus Cancer	
Factors Influencing Risk	Estimated Relative Risk*
Older age	2-3
Residency in North America or Northern Europe	3-18
Higher level of education or income	1.5-2
White race	2
Nulliparity	3
History of infertility	2-3
Menstrual irregularities	1.5
Late age at natural menopause	2-3
Early age at menarche	1.5-2
Long-term use of unopposed estrogen	10-20
Tamoxifen use	2-3 [†]
Obesity	2-5
Estrogen-producing tumor	>5
History of type 2 diabetes, hypertension, gallbladder disease, or thyroid disease	1.3-3
Lynch syndrome	6-20 [‡]

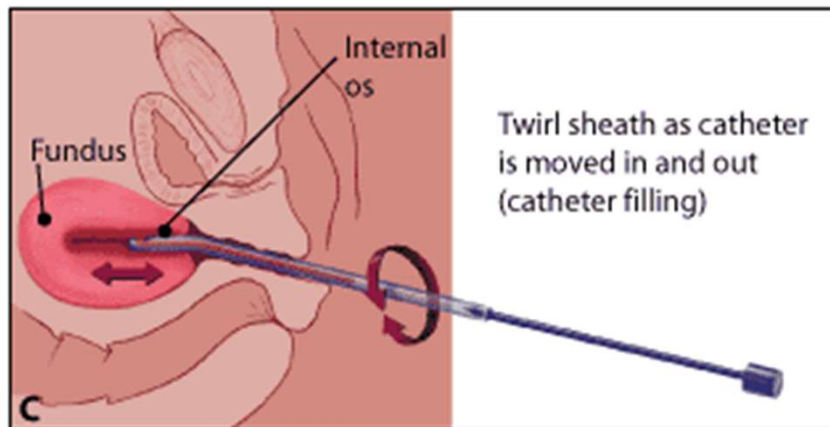
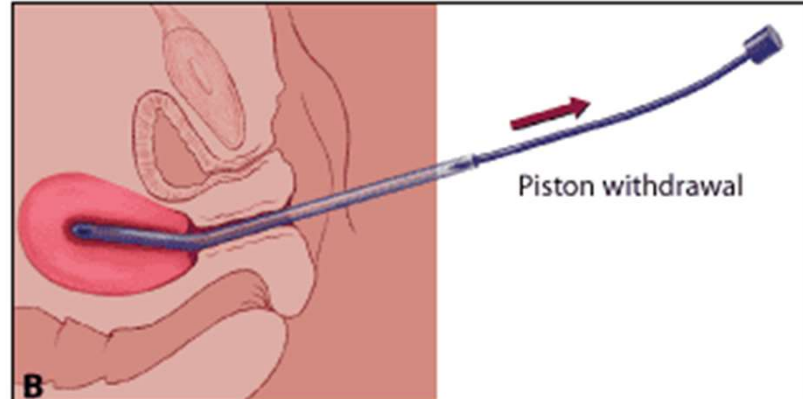
EMB: THE PROCEDURE



Endometrial suction catheter.



© 2001 Renee L. Cannon



(A) The catheter tip is inserted into the uterus fundus or until resistance is felt. (B) Once the catheter is in the uterus cavity, the internal piston is fully withdrawn. (C) A 360-degree twisting motion is used as the catheter is moved between the uterus fundus and the internal os.

EMB: SUCTION DEVICES

- Low Pressure

Pipelle Endometrial Suction Curette



- High Pressure



Uterine Explora Curette: Model I w/ Vacu-Lok Syringe



EMB: BENEFITS

- Less invasive
- Safe
- Less expensive
- Performed in outpatient setting in the office
- No anesthesia or local anesthesia for pain control

EMB: RISKS

- Pain
- Bleeding
- Infection
- Uterine Perforation
- Injury to nearby structures (nerves, vessels, bowel, bladder, ureter)

EMB: LIMITATIONS

- Sensitivity influenced by
 - Type of lesion (focal or diffuse)
 - Pathologic diagnosis (intracavitary leiomyoma or polyp)
 - Size and number of lesion
 - Presence of uterine malformation
 - Surface area of the endometrial cavity

- Endometrium sample size: 4% of endometrium (range of 0-12%)

Risk Factors for Unsuccessful Office-Based Endometrial Biopsy: A Comparative Study of Office-Based Endometrial Biopsy (Pipelle) and Diagnostic Dilatation and Curettage

Bingying Xie MD, Cuifeng Qian MD, Bingyi Yang MD, Chengcheng Ning MD, Xiaoying Yao MD, Yan Du PhD, Yue Shi MD, Xuezhen Luo MD, PhD and Xiaojun Chen MD, PhD

Journal of Minimally Invasive Gynecology, The, 2018-05-01, Volume 25, Issue 4, Pages 724-729, Copyright © 2018

- Risk factors for failure:
 - Postmenopausal duration
 - History of cervical operations
 - Pinpoint cervical os (external cervical orifice < 1 mm in diameter)
 - Absence of prior intrauterine procedures

- Risk factors for sample inadequacy:
 - Menopausal status
 - Endometrial thickness < 7mm
 - Uterine volume > 43 cm³

EMB: ALTERNATIVES

- Office Hysteroscopy
- Transvaginal Ultrasound
 - Ideally performed between day 4-6 of the menstrual cycle
 - No established endometrial thickness defined as abnormal for premenopausal patients
- Saline Infusion Sonohysterogram

The Time Has Come to Quit Relying on a Blind Endometrial Biopsy or Dilation and Curettage to Rule Out Malignant Endometrial Changes

Franklin D. Loffer MD, FACOG

Journal of Minimally Invasive Gynecology, The, 2019-11-01, Volume 26, Issue 7, Pages 1207-1208, Copyright © 2019

- Visually directed biopsy as an alternative
- 

ASSESSMENT IN PREMENOPAUSE



ASSESSMENT IN PREMENOPAUSE

13-18
years old

19-39
years old

40 years old to
menopause

ASSESSMENT IN PREMENOPAUSE

- **13-18 years old**

- In 2005-2009, endometrial cancer incidence < 20 years old was 0.2 per 100,000 women

Clinical History:

- 2-3 years of abnormal bleeding
- Obesity
- Failed medical treatment after investigation of other causes

ASSESSMENT IN PREMENOPAUSE

- **19-39 years old**

- Endometrial cancer risk is still low
 - 20-34 years old – 1.6%
 - 35-44 years old – 6.2%

Clinical History:

- Nulliparity
- Hypertension
- BMI >30
- Irregular menstruation with prolonged unopposed estrogen
- Family history
- Failed response to medical therapy

ASSESSMENT IN PREMENOPAUSE

- **40 years old to menopause**

- Endometrial cancer risk

- 40-50 years old: 13.6 to 24 cases per 100,000 women

Clinical History:

- All women older than 45 years old with suspected anovulatory bleeding should be evaluated

Prediction of Endometrial Hyperplasia and Cancer among Premenopausal Women with Abnormal Uterine Bleeding

Giannella, Luca; Lillo Bruno Cerami; Setti, Tiziano; Bergamini, Ezio; Boselli, Fausto.

BioMed Research International; New York Vol. 2019, (2019). DOI:10.1155/2019/8598152

- Objective: create a prediction model for clinical variables for prediction of premalignant/malignant pathology in premenopausal women with abnormal uterine bleeding

- Observational retrospective study including 240 premenopausal women referred to diagnostic hysteroscopy
 - 12 women (5%) had endometrial hyperplasia or cancer
 - Stepwise logistic regression analysis showed association was significant with
 - BMI \geq 30 (OR=7.70, 95% CI 1.90 to 31.17)
 - Diabetes (OR=9.71, 95% CI 1.63 to 57.81)
 - Thickened endometrium (OR=1.20, 95% CI 1.08 to 1.34, criterion > 11 mm)

CONCLUSION



CONCLUSION

- Risk factors for the development of endometrial hyperplasia and malignancy
 - Nulliparity
 - Early menarche
 - Late menopause
 - History of Infertility
 - Obesity (BMI >30)
 - Chronic anovulation/Menstrual irregularities
 - Older age
 - History of T2DM, Hypertension, gallbladder disease, or thyroid disease
 - Residency in North America or Northern Europe
 - Higher level of education or income
 - White race
 - Unopposed estrogen
 - Tamoxifen use
 - Estrogen-producing tumor
 - Failed Medical Management
 - Lynch Syndrome/Cowden disease

CONCLUSION

- Endometrial biopsy procedure

CONCLUSION

- Consider the benefits, risks, limitations, and alternatives to an endometrial biopsy when evaluating abnormal uterine bleeding in the premenopausal patients

ASSESSMENT IN PREMENOPAUSE

13-18
years old

19-39
years old

40 years old to
menopause

QUESTIONS



REFERENCES



REFERENCES

Baggish MS, Valle RF, Guedj H. Hysteroscopy: Visual perspectives of uterine anatomy, physiology and pathology. Philadelphia: Lippincott Williams & Wilkins (2007). Retrieved on October 26, 2019 from UpToDate.

Committee Opinion 631: Endometrial Intraepithelial Neoplasia. May 2015. *Obstet Gynecol* 2015;125:1272–8

Del Priore MD, MPH, G. Endometrial sampling procedures. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <https://www.uptodate.com> (Accessed on October 26, 2019.)

Endometrial Cancer Screening Guidelines. Retrieved from <https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/endometrial-cancer-screening-guidelines.html>

Giannella, L.; Cerami, L.B.; Setti, T.; Bergamini, E.; Boselli, F. (2019). Prediction of endometrial hyperplasia and cancer among premenopausal women with abnormal uterine bleeding. *BioMed Research International*. doi: 10.1155/2019/8598152. eCollection 2019.

Hysteronews. Hysteroscopic pictures of endometrial cancer [Online image]. (2018). Retrieved on October 26, 2019 from <https://hysteroscopynewsletter.com/2018/09/02/hysteroscopic-pictures-of-endometrial-cancer/>

Indman. View of uterus through a hysteroscope [Online image]. (2011). Accessed October 26, 2019. Retrieved from <https://www.obgyn.net/fibroids/diagnosis-uterine-fibroids>

REFERENCES

Kaunitz MD, A.M. Approach to abnormal uterine bleeding in nonpregnant reproductive-age women. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <https://www.uptodate.com> (Accessed on October 26, 2019.)

Loffer MD, F.D. (2019). The time has come to quit relying on a blind endometrial biopsy or dilation and curettage to rule out malignant endometrial changes. *Journal of Minimally Invasive Gynecology*; 26(7):1207-1208. doi: 10.1016/j.jmig.2019.04.011. Epub 2019 Apr 10

Practice bulletin 149: Endometrial cancer. April 2015. *Obstet Gynecol* 2015; 125: pp. 1006-1026

Practice bulletin 136: Management of abnormal uterine bleeding associated with ovulatory dysfunction. July 2013. *Obstet Gynecol* 2013; 122: pp. 176-85

Welt MD, C.K.. Physiology of the normal menstrual cycle. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <https://www.uptodate.com> (Accessed on October 26, 2019.)

Xie MD, B., Qian, C., Yang, B., Ning, C., Yao, X., Du, Y., Shi, Y., Luo, X., Chen, X. (2018). Risk Factors for Unsuccessful Office-Based Endometrial Biopsy: A Comparative Study of Office-Based Endometrial Biopsy (Pipelle) and Diagnostic Dilation and Curettage. *Journal of Minimally Invasive Gynecology*; 25 (4): p724-729. doi: 10.1016/j.jmig.2017.11.018. Epub 2017 Dec 6.

Zuber MD, T.J. (2001). Endometrial Biopsy. *Am Fam Physician*. 63(6):1131-1135.

THANK YOU!

