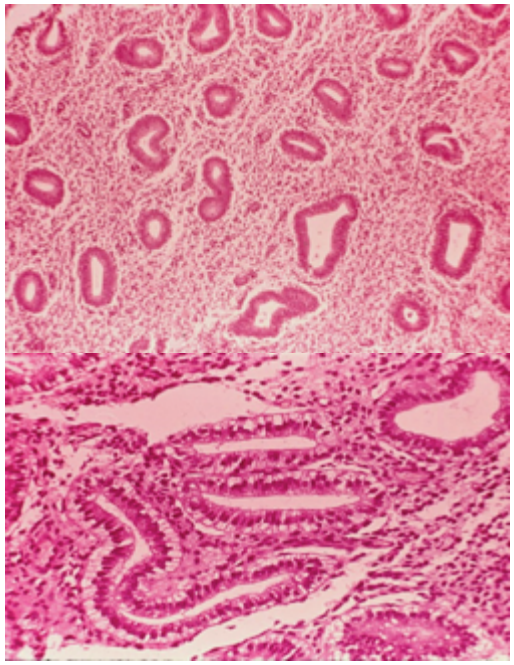
UTERUS ENDOMETRIUM

ENDOMETRIAL CYCLE

- Menses: superficial endometrium (functionalis) is shed
- **PROLIFERATIVE PHASE:** rapid growth of glands (tubular glands, pseudostratified columnar epithelium, mitotic figures) & stroma
- **OVULATION:** proliferation ceases, differentiation begins (response to progesterone)
- **SECRETORY PHASE:** subnuclear vacuoles, which move more apically as secretory phase progresses; late secretory phase glands become dilated & serrated & stroma shows prominent spiral arteries, increase in cytoplasmic eosinophilia (predecidual change), sparse infiltrate of polys & lymphs
- As corpus luteum ceases functioning, progesterone levels fall & functionalis degenerates & menses ensure



PROLIFERATIVE ENDOMETRIUM

SECRETORY ENDOMETRIUM

1. DYSFUNCTIONAL UTERINE BLEEDING

DEFINITION

Applies to *bleeding* without an underlying structural cause, most commonly occurring at **menarche & peri-menopausal ages**
May take the form of *menorrhagia, metrorrhagia, or post-partum bleeding*;

ANOVULATORY CYCLE **is the most common cause**, but may also be from endocrine disorders, ovarian lesions, & generalized metabolic disorders.
Results from relatively **unopposed estrogen excess**. Biopsy may show ***age & cycle-dependent abnormalities in maturation***.

(FYI*: Anovulatory Cycle: a menstrual cycle characterized by varying degrees of menstrual intervals & the absence of ovulation & a luteal phase.)*

INADEQUATE LUTEAL PHASE: manifest clinically as ***infertility & amenorrhea;*** **inadequate progesterone during post-ovulatory period.** Biopsy may ***show secretory endometrium lagging in maturity for expected menstrual date.***

CLINICAL

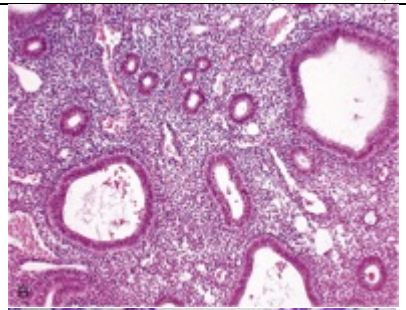
Irregular, heavy bleeding

PATHOGENESIS

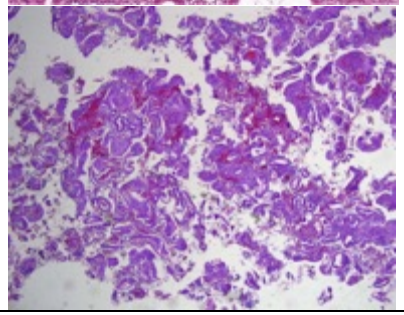
Causes can be broken down as they vary with Age & Hormonal Development:

- **PRE-PUBERTY:** precocious puberty – *hypothalamic, pituitary, or ovarian origin*
- **ADOLESCENCE:** anovulatory cycle
- **REPRODUCTIVE AGE:**
  - Complications of pregnancy – *abortion, trophoblastic disease, ectopic pregnancy*
  - Proliferations – *leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma*
  - Anovulatory cycle: caused by anything that leads to excess estrogen relative to progesterone – *hypothalamic, adrenal,* ***thyroid dysfunction****, functional ovarian lesions with excess estrogens,* ***malnutrition****,* ***obesity****-debilitating disease, severe emotional distress*
  - Ovulatory dysfunctional bleeding: corpus lutem fails to mature → relative excess progesterone
  - Endomyometrial dysorders – *submucosal leiomyomas, endometritis, endometrial polyps*

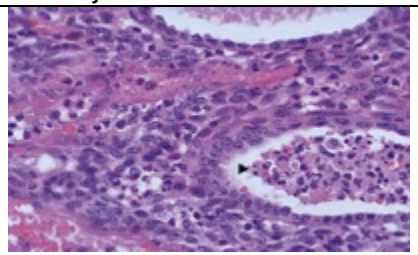
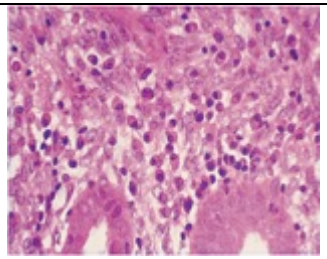
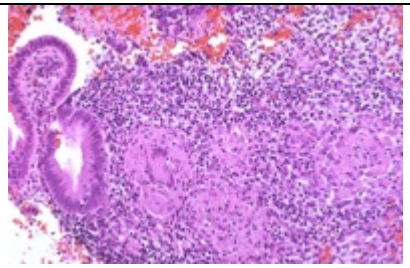
MORPHOLOGY

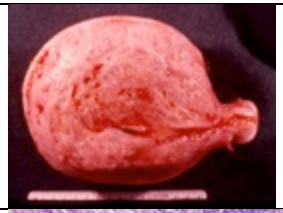
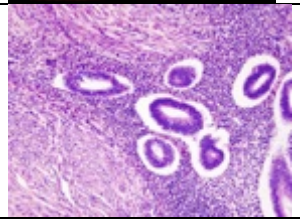


Anovulatory Endometrium: a scattered distribution "regularly irregular" of cystically-dilated proliferative glands is caused by excess estrogen exposure. There are some non-discrete clusters of glands.



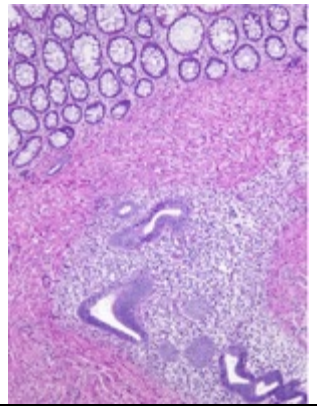
Typical pattern of Dysfunctional Bleeding: mostly **stromal breakdown** & scattered glands & surface epithelium.

	2. ACUTE ENDOMETRITIS Post-Delivery or Miscarriage	3. CHRONIC ENDOMETRITIS	4. GRANULOMATOUS ENDOMETRITIS
DEFINITION	Acute glandular & stromal inflammation		
CLINICAL	Fever, abnormal bleeding, & pelvic pain **AFTER DELIVERY**	*Fever, pain, menstrual abnormalities* ***↑Risk of infertility due to scarring & fallopian tube involvement***	
PATHOGENESIS	Bacterial infections from **complications of childbirth** – **Group A Strep & Staph are most common** – Can also be related to Chlamydia infection ***Retained products of conception after delivery increase risk of endometritis.***	Often secondary to *N. gonorrhea* or *C. trachomatis* **(PELVIC INFLAMMATORY DISEASE)** May be secondary to *retained products of conception* or other *foreign bodies* (***IUD***)	
MORPHOLOGY	 Scattered **neutrophils** within endometrial glands & stroma, indicative of **acute endometritis**.	 ***PRESENCE OF PLASMA CELLS**	

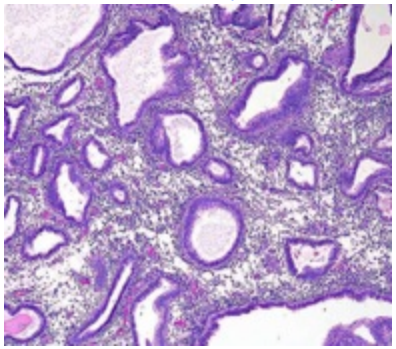
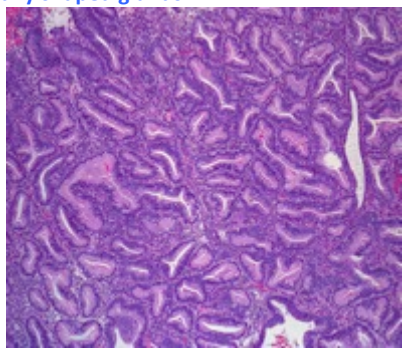
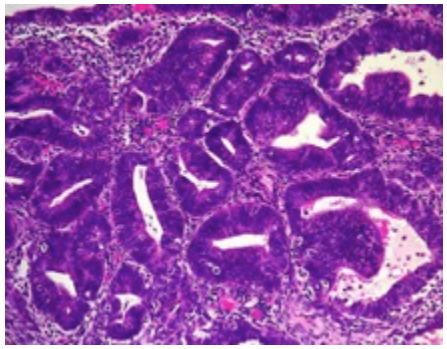
5. ADENOMYOSIS – "Endometriosis of the Myometrium"	
DEFINITION	Adenomyosis occurs when endometrial tissue, which normally lines the uterus, exists within and grows into the muscular wall of the uterus. (Mayo Clinic)
CLINICAL	**Menorrhagia** *(abnormally heavy bleeding)*, dysmenorrhea, **pelvic pain preceding menses**
GROSS	 **SYMMETRIC enlargement of the uterus**
MORPHOLOGY	 Growth of **BASAL LAYER of endometrium** **into the myometrium** Reactive hypertrophy of surrounding stroma → **enlarged uterus** *Basal layer does not undergo cyclic changes*
TREATMENT	**IRRESPONSIVE to estrogen**

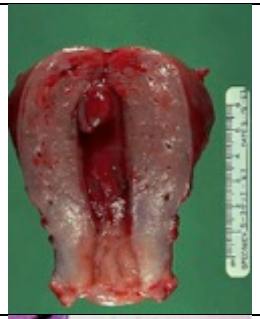
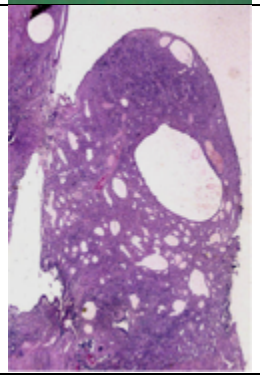
6. ENDOMETRIOSIS

10% of women of reproductive age

DEFINITION	Endometrial glands & stroma outside of endometrium – ***ectopic endometrial tissue*** *in ovaries, fallopian tubes, broad ligaments, vagina, peritoneum, bladder, etc.* **Differs from normal endometrium:** – ↑ Levels of inflammatory mediators (PGE2) – ↑ Estrogen production due to high aromatase activity in stroma
CLINICAL	**Dysmenorrhea & pelvic pain** from peri-uterine bleeding & adhesions – ultimately may lead to **INFERTILITY** *Endometrial glands can respond to ovarian hormones so that cyclic abdominal pain coincides with menstruation.* (Robbins)
PATHOGENESIS	Regurgitation Theory, Metaplastic Theory, Vascular or Lymphatic Dissemination Theory, Extrauterine Progenitor Cell Theory *PTEN, ARID1A mutation*
GROSS	**RED-BROWN**, 1-2 mm nodules usually on **serosal surface**; may coalesce into larger **"CHOCOLATE CYST"** *(A focus of endometriosis that becomes an expanding cystic lesion as its center becomes filled with chocolate-brown sludge from recurrent hemorrhage. Robbins)*
MORPHOLOGY	**Lesions must contain ENDOMETRIAL STROMA, GLANDS, & HEMOSIDERIN** **Secondary fibrosis & scarring may occur** **With extensive bleeding – ADHESIONS & scarring of fallopian tubes (*infertility*)**  Endometrial glands & stroma are present in this section of **large intestine**
COURSE/ TREATMENT	*Association with endometriosis & ovarian cancer exists* ***(3-fold increased risk of carcinoma)*** **TX: COX-2 Inhibitors + Aromatase Inhibitors**

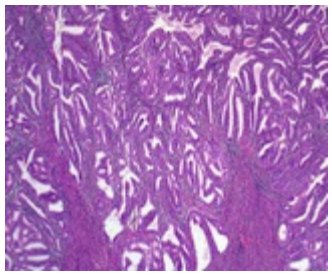
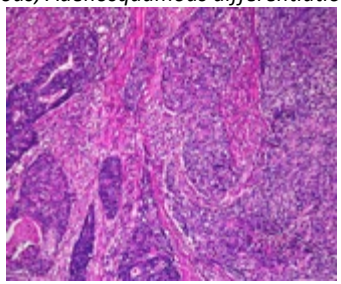
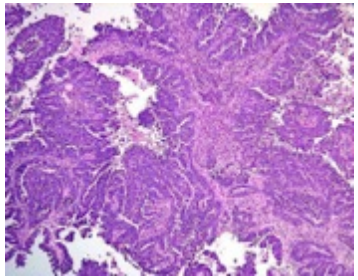
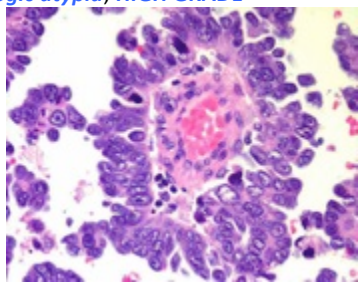
7. ENDOMETRIAL HYPERPLASIA

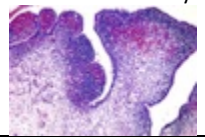
DEFINITION	**Prolonged excess of UNOPPOSED estrogen; *pre-cursor of carcinoma***
CLINICAL	***Abnormal bleeding*** near menarche or in post-menopausal women
PATHOGENESIS	**PTEN inactivation** *(common abnormality & important in progression to carcinoma)* **Excess estrogen caused by:** – Failure of ovulation (per-menopause) – Prolonged estrogen therapy – Estrogen-producing ovarian tumors – **Obesity**: *increased adipocyte conversion of androgens to estrogen* – PCOS
MORPHOLOGY	**Increased # of glands relative to stroma; crowded, abnormally shaped glands**  **SIMPLE HYPERPLASIA**  **COMPLEX HYPERPLASIA**  **COMPLEX HYPERPLASIA W/ ATYPIA**
COURSE/ TREATMENT	**Non-atypical hyperplasia *rarely progresses to cancer*** **ATYPICAL HYPERPLASIA (endometrial intraepithelial hyperplasia) is *frequently associated with cancer***

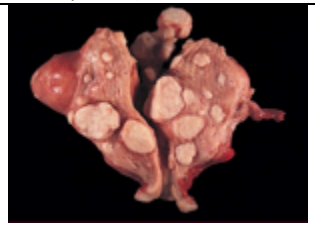
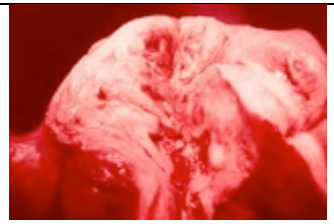
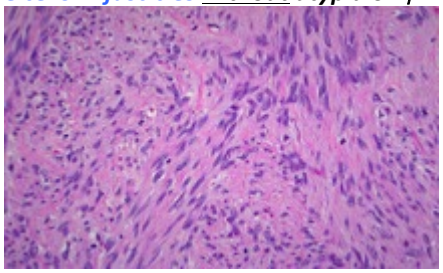
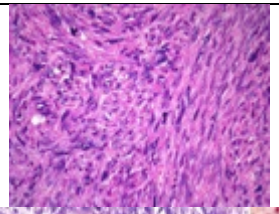
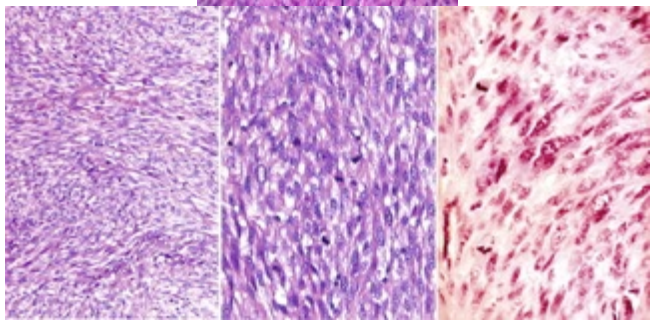
8. ENDOMETRIAL POLYPS Most common in Peri-menopause	
DEFINITION	Benign proliferation of hyperplastic endometrial stroma
CLINICAL	*Abnormal, heavy bleeding*
PATHOGENESIS	Stromal cells are monoclonal with 6p21 rearrangement
GROSS	 Sessile 0.5-3cm, large polyps – ***may protrude into uterine cavity***
MORPHOLOGY	 Stroma, glands with cystic dilation, & prominent vessels
COURSE/ TREATMENT	**RARELY lead to cancer**

ENDOMETRIAL CARCINOMA

- *Staging based on how far tumor has gone through myometrium or involved other structures*
  - IA: tumor is only in the endometrium or less than halfway through myometrium
  - IB: tumor is more than half way through the myometrium, but still contained in uterus
  - II: tumor has reached the CT of the cervix but has not spread outside the uterus
  - IIIA: tumor has reached the outer layer of the uterus and/or the ovaries, fallopian tubes, or ligaments of the uterus

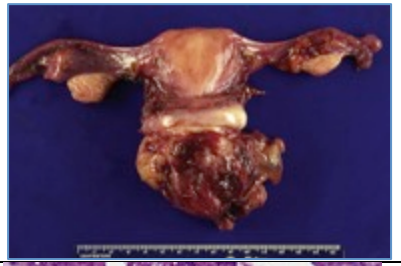
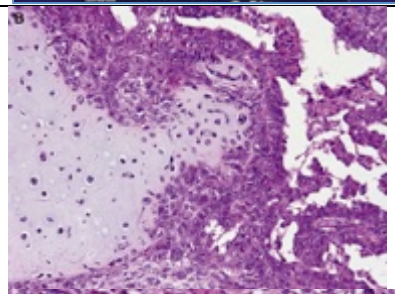
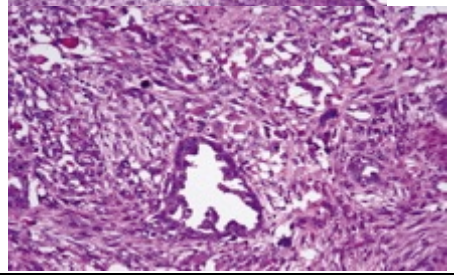
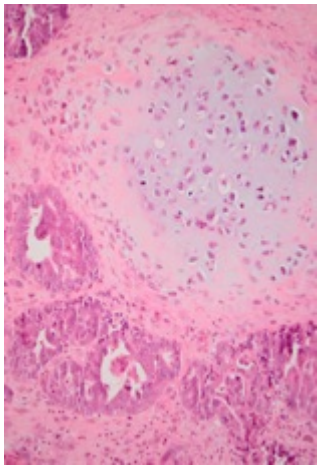
	9. ENDOMETRIOID ADENOCARCINOMA (Type I Endometrial Carcinoma) ***Most common endometrial carcinoma*** **55-66 years old** *(rare before 40)*	**10. SEROUS ADENOCARCINOMA (Type 2 Endometrial Carcinoma)** **65-75 years old**
DEFINITION	Arises from **ATYPICAL HYPERPLASIA**; **GLANDULAR** structures closely resemble normal endometrial glands histologically	Arises from **ATROPHIC ENDOMETRIUM**; ***Clear Cell Carcinoma & Mixed Mullerian Tumors are also included in this category***
CLINICAL	**LEUKORRHEA, irregular bleeding, enlarged uterus** Detected by ***post-menopausal bleeding***	
RISK FACTORS	**OBESITY**, diabetes, HTN, infertility, unopposed estrogen therapy, estrogen producing ovarian tumors (hyperestrogenism)	*NOT associated with any other the RFs listed to the right*
PATHOGENESIS	Mutations in **mismatch repair genes & PTEN** – Common **[COWDEN SYNDROME: germline mutations of PTEN]** PTEN mutation → activates KRAS, **PIK3CA**, or inactivates PTEN → activation of AKT: *cell cycle dysregulation, blocked apoptosis, mTOR activation*	Mutations in **p53** – Common ****DNA mismatch repair genes & PTEN are usually NORMAL!***
MORPHOLOGY	Histologic Types: *Mucinous, Tubal, Squamous, Adenosquamous differentiation*  **WELL-DIFFERENTIATED (GRADE 1)**  **POORLY-DIFFERENTIATED (GRADE 3)**	Form small tufts & **papillae**, ***marked cytologic atypia***; **HIGH GRADE**  
COURSE	Good prognosis	Aggressive behavior → **POOR PROGNOSIS**

11. ENDOMETRIAL ADENOSARCOMA	12. ENDOMETRIAL STROMAL TUMORS	13. MULLERIAN ADENOSARCOMA
Women in 4th & 5th decades Broad-based polypoid growths that prolapse through cervical os Malignant stroma & benign glands	Benign stromal nodules, low grade stromal sarcomas, high grade stromal sarcomas Low-grade associated with fusion of JAZF1 gene & polycomb factor genes (SUZ12)	Intraglandular papillae are composed of sarcomatous stroma that is more cellular beneath the benign-appearing glandular epihelium, resulting in a cambium-like layer. 

	14. LEIOMYOMA (AKA Fibroids) *Most common tumor of Reproductive age* Blacks > Whites	15. LEIOMYOSARCOMA Post-menopausal Women
DEFINITION	**BENIGN** uterine smooth muscle tumors due to **increased estrogen exposure**	**MALIGNANT** tumor of uterine smooth muscle that **arises *de novo*** (NOT from pre-existing leiomyomas)
CLINICAL	***Often asymptomatic****; may present with menorrhagia +/- metrorrhagia; sometimes palpable; often causing* ***'dragging sensation'*** *in pelvis (pain + pressure)*	*Abdominal discomfort or bloating,* ***post-menopausal bleeding***
PATHOGENESIS	Monoclonal tumors w/ rearrangements on **chromosomes 6 & 12** ***Estrogen*** *& oral contraceptives may stimulate growth* (this is why the shrink post-menopause!)	MED12 mutation
GROSS	 **MULTIPLE, WELL-DEMARCATED, FIRM GREY-WHITE WHORLED NODULES**	 **SINGLE TUMOR W/ POORLY-DEFINED MARGINS** **+ HEMORRHAGE & NECROSIS**
MORPHOLOGY	Submucosal, intramurual, or subserosal in location **Bundles of smooth muscle cells with foci of fibrosis** ***Spindle cells in fascicles without atypia or ↑mitoses*** 	**DIAGNOSTIC CRITERIA:** 1. **NECROSIS** 2. **CYTOLOGIC ATYPIA** 3. **MITOTIC ACTIVITY**   **LEFT:** Highly cellular tumor w/ **spindle cells in intersecting fascicles** **CENTER:** Higher magnification of same tumor showing diffuse ***severe atypia & mitotic figures.*** Atypical cells show only mild variation in size & shape. **RIGHT:** A different tumor showing ***diffuse severe atypia*** & mitotic figures. In contrast to the previous tumor, there is marked ***nuclear pleomorphism*****.**
COURSE/ TREATMENT	**Almost NEVER progresses to malignancy**	**Recurrence after resection & distant metastasis (LUNG) are common**

16. MALIGNANT MIXED MULLERIAN TUMORS – MMMTs (AKA Carcinosarcomas)

Post-menopausal Women

DEFINITION	Endometrial adenocarcinoma with a malignant mesenchymal component **(Endometrial Carcinoma + Stromal Sarcoma)** Mesenchymal component may be homogenous (stromal or smooth muscle) or heterologous (rhabdo or chondrosarcoma)
CLINICAL	***Post-menopausal bleeding + pain***
PATHOGENESIS	Same genes mutated as in Endometrial Adenocarcinoma: **PTEN, TP53, PIK3CA** *(suggests these are carcinomas w/ sarcomatous differentiation)*
GROSS	 **Large, polypoid & hemorrhagic tumor** **protruding through the cervical os**
MORPHOLOGY	 Different components that can ***mimic uterine or extrauterine tissue***  MMMT composed of **rhabdomyosarcoma** & shows only focal epithelial differentiation **POOR PROGNOSIS* 
COURSE	**Tumor STAGE is the most important prognostic factor** ****Endometrial hyperplasia, Endometrial intraepithelial carcinoma, or Endometroid/Serous Carcinoma in the adjacent endometrium is seen in up to 50% of cases***