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This slide contains the learning objectives for the presentation. The title 'Learning Objectives' is in blue font at the top left. Below it, a green box contains three bullet points in white text. To the right of the green box, there are two histological images of endometrial tissue stained with H&E. The top image shows a cross-section of the endometrium with glandular structures, and the bottom image shows a higher magnification view of the glandular epithelium. The copyright notice '© College of American Pathologists.' is at the bottom left.

Learning Objectives

- Revisit patterns of normal menstrual cycle.
- Compare and contrast normal and abnormal hormonal alterations of the endometrium.
- Recognize specific constellations of features to diagnose specific benign conditions of the endometrium.

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Algorithm to describe findings

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Development of Endometrium

Uniform

- Proliferative phase
- Early and midsecretory phase
- Inactive/atrophy
- Oral contraceptives

Variable

- Endometritis
- Late secretory phase
- Pregnancy
- Disordered prolif.
- Polyp
- Hyperplasia

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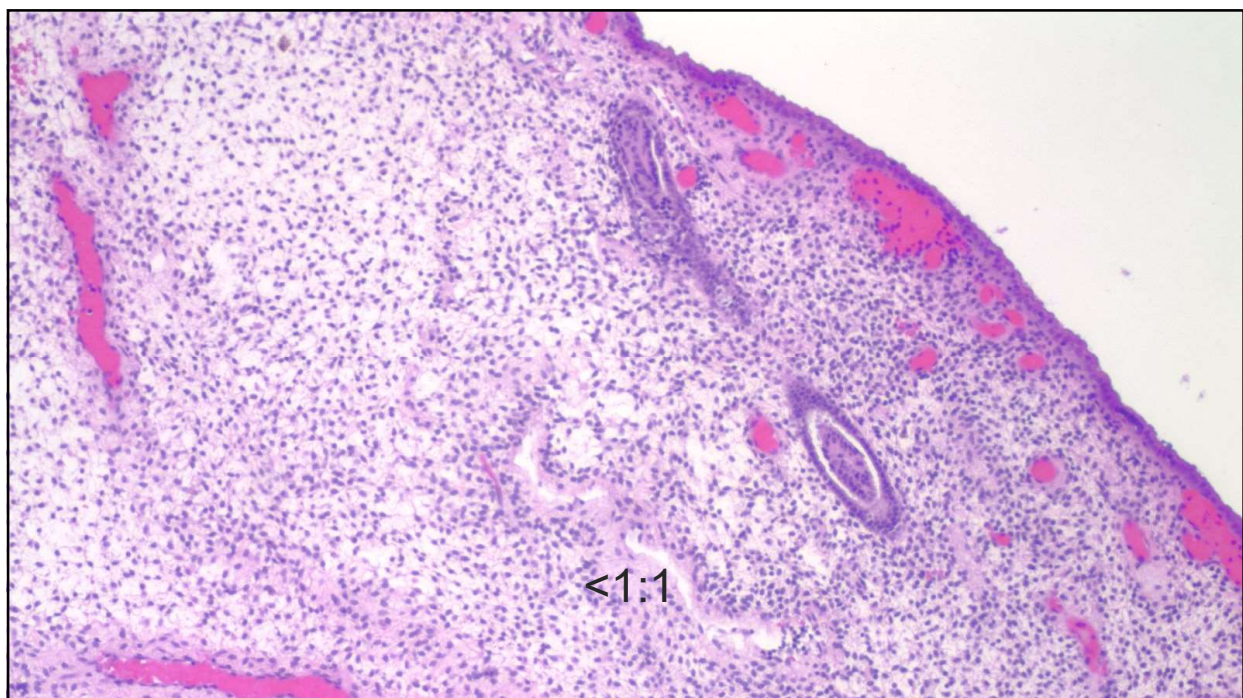
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Gland:stromal ratio

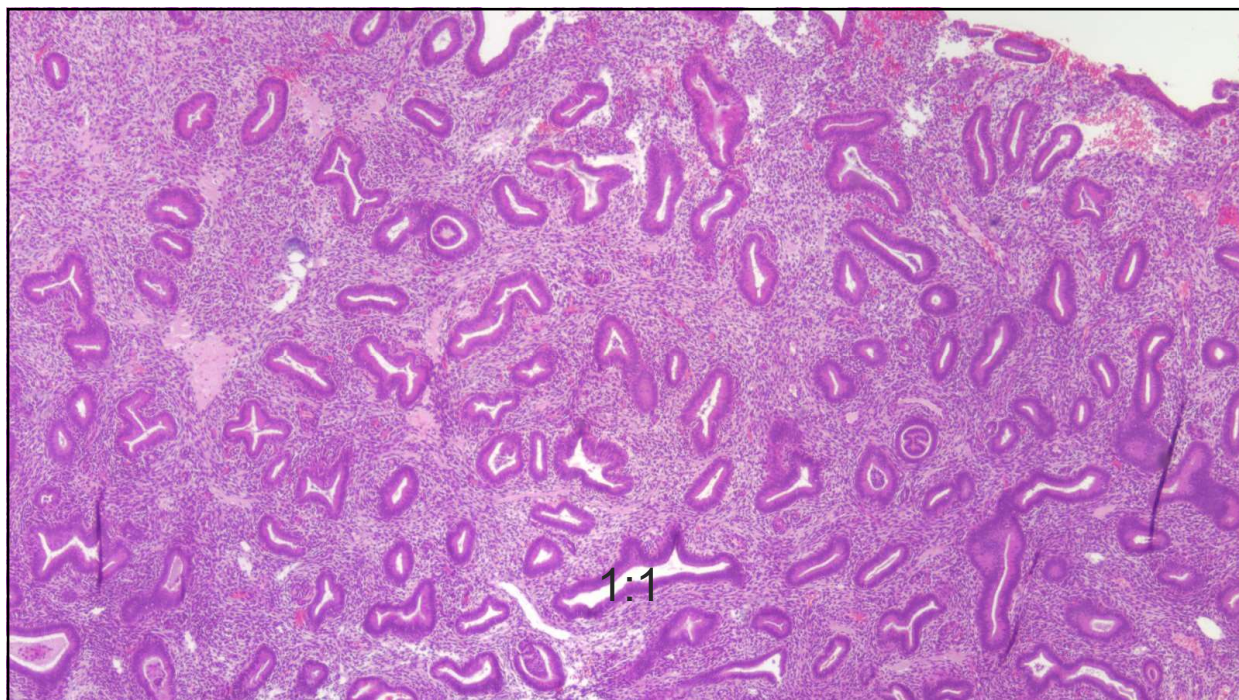
<1:1	1:1	>1:1
Early proliferative	Mid/late proliferative	Midsecretory
Inactive/atrophy	Early secretory	Hyperplasia
Progestin Rx	Late secretory	Carcinoma
OCs		

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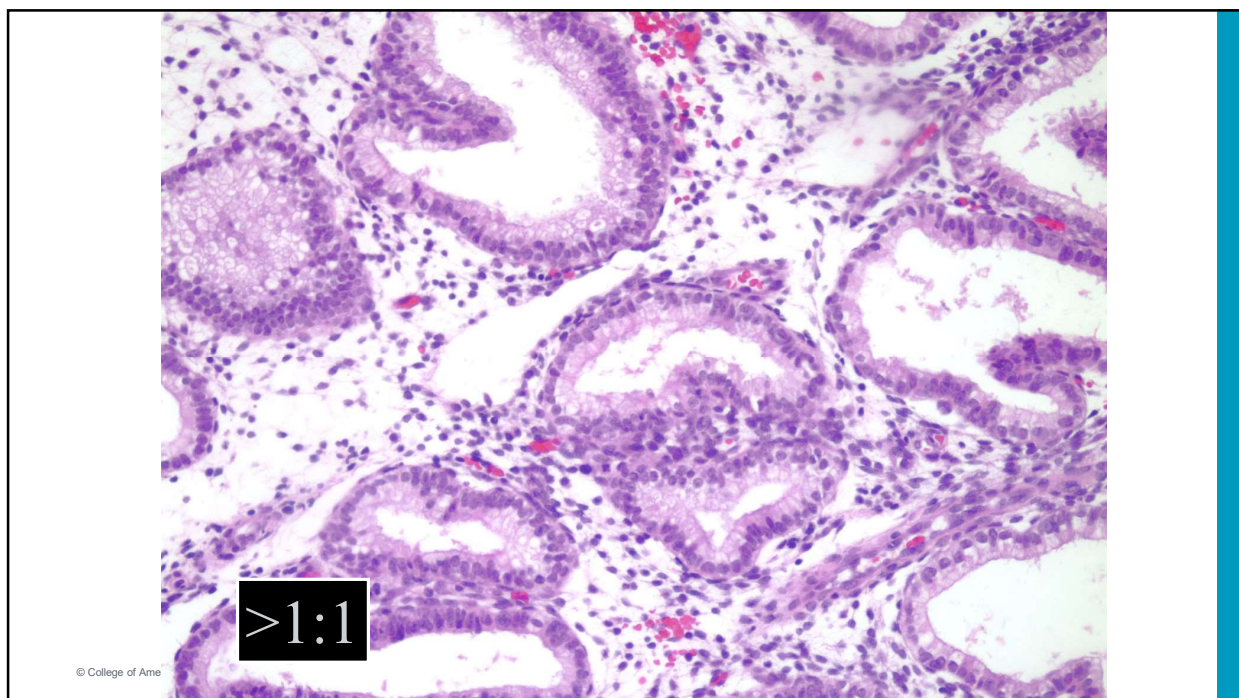
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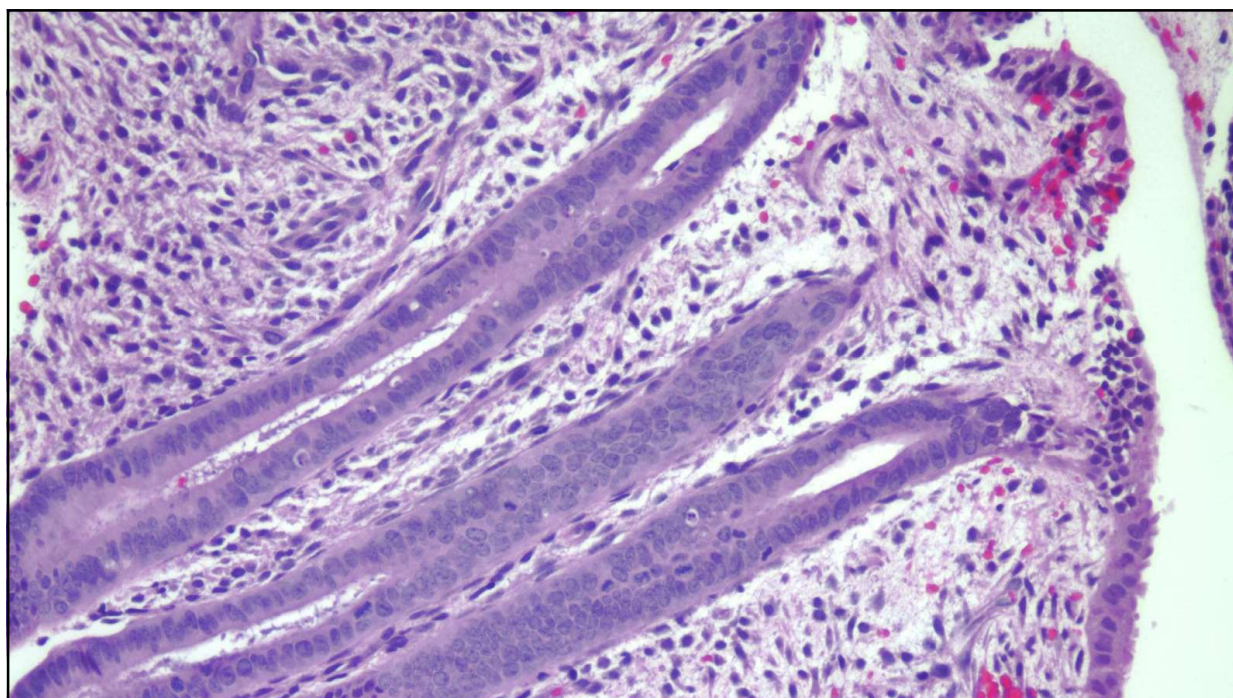


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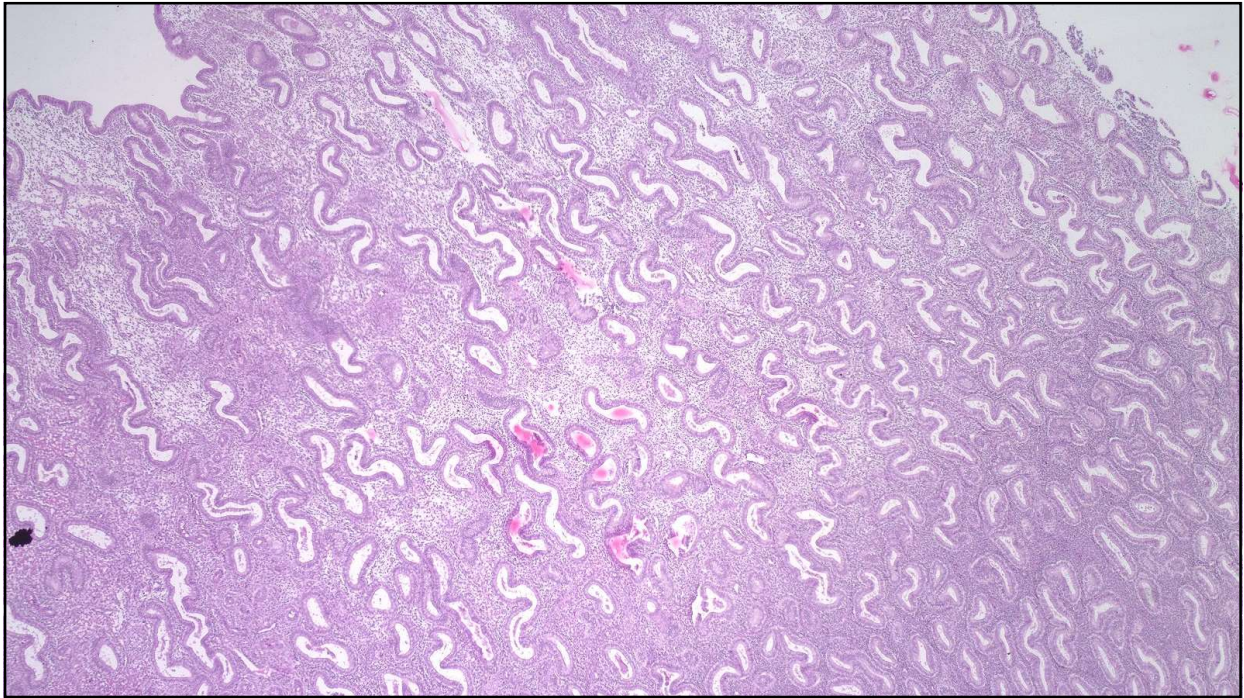
Glandular configuration

Straight	Coiled	Dilated	Serrated	Branching
Early proliferative	Late proliferative	Midsecretory	Late secretory	Disordered
Midproliferative	Early secretory	Polyp	Pregnancy	Hyperplasia
OCs		Cystic atrophy		Carcinoma
Progestin Rx				
Atrophy				

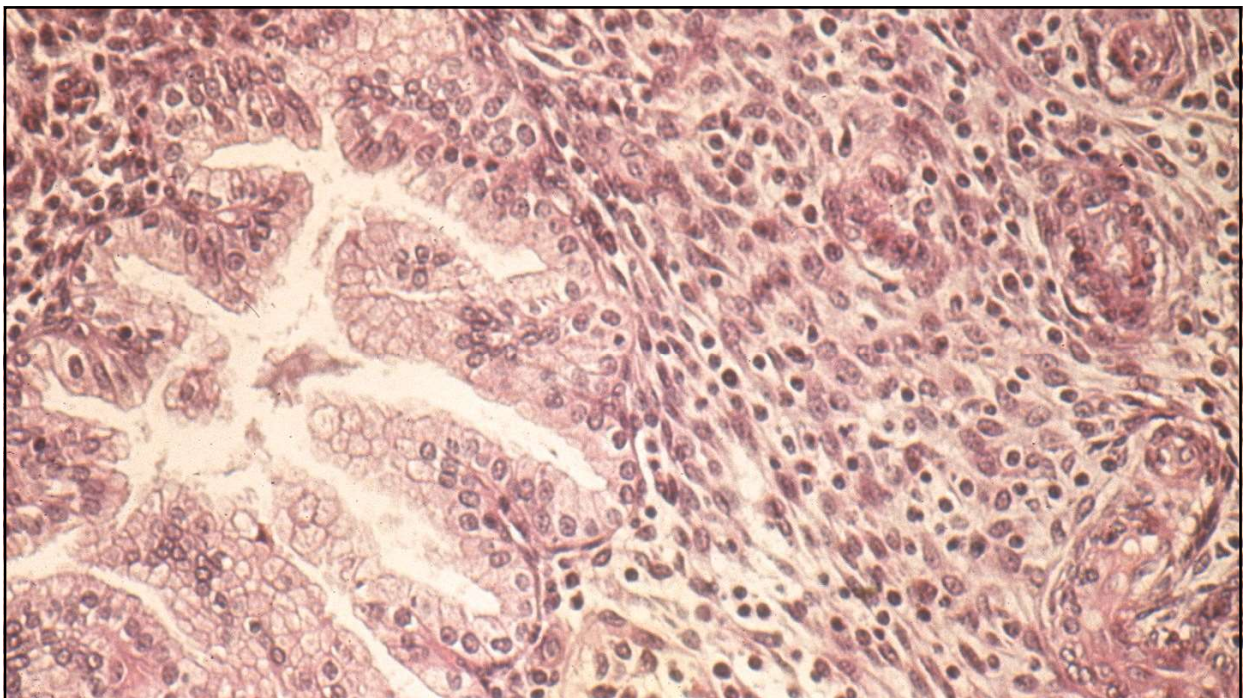
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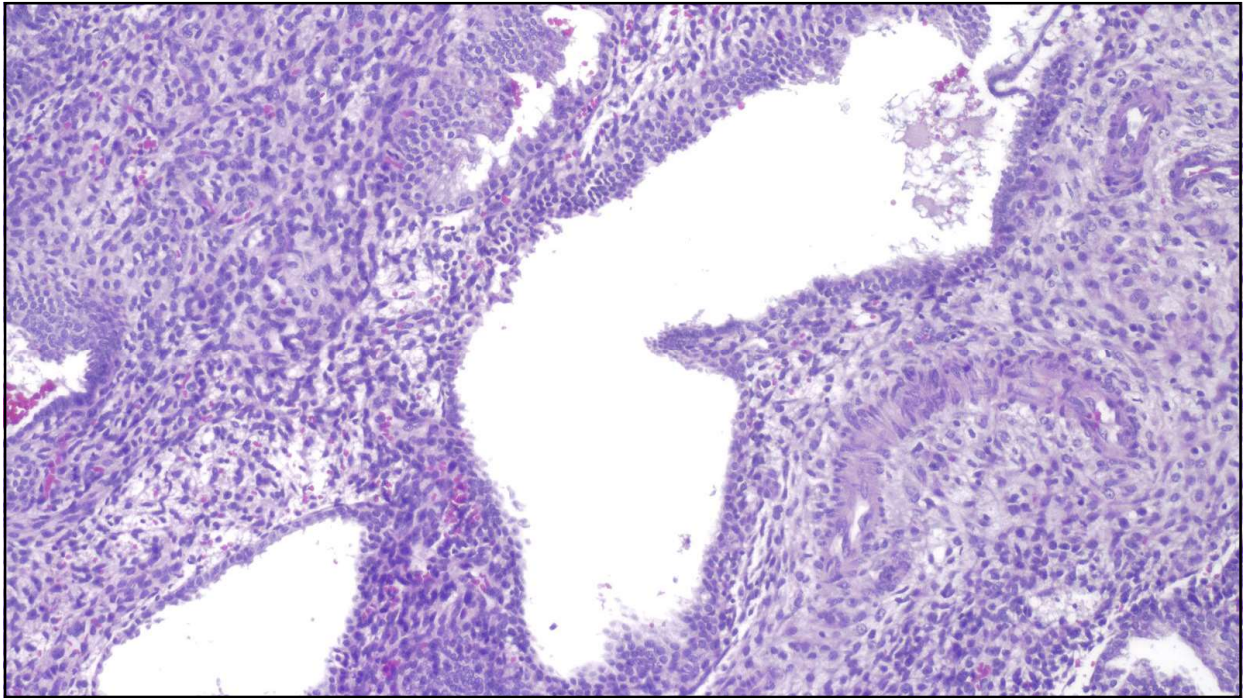
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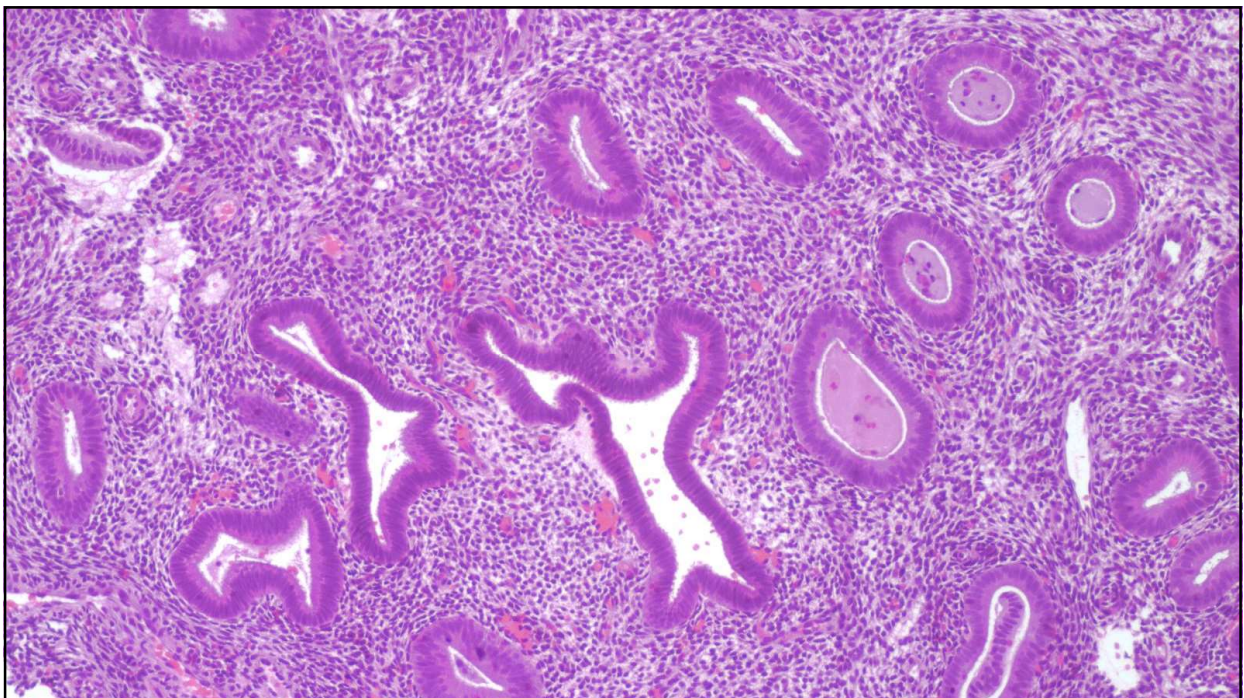
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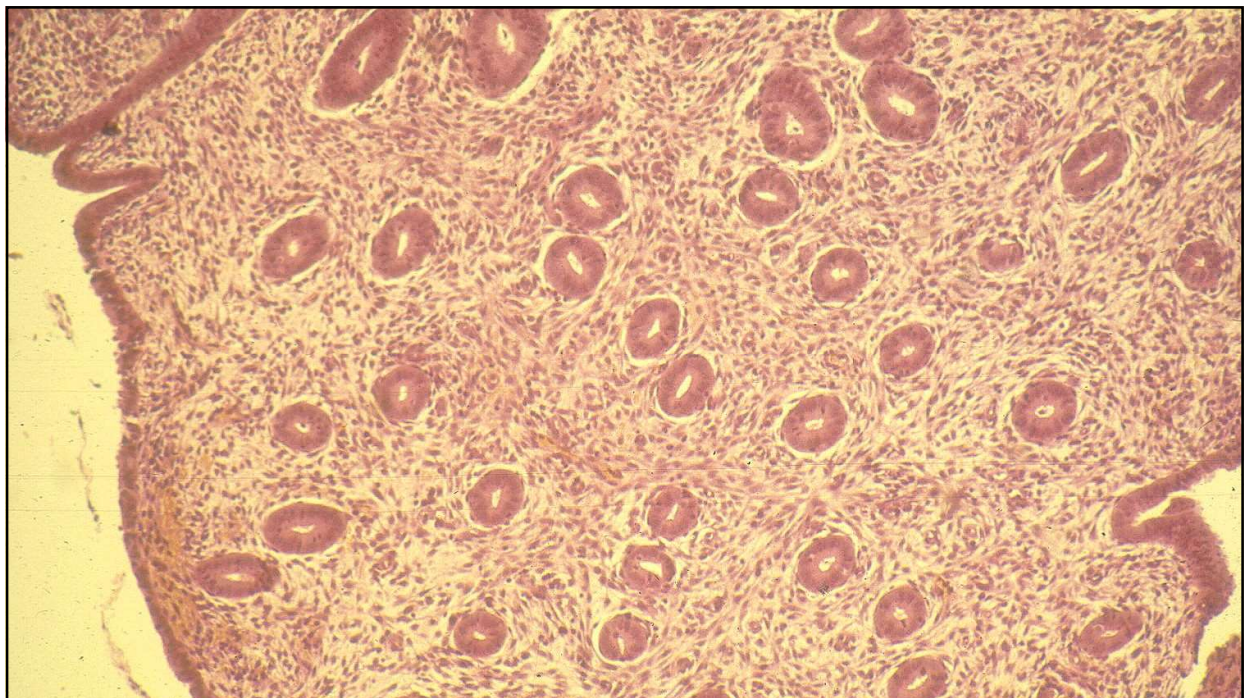


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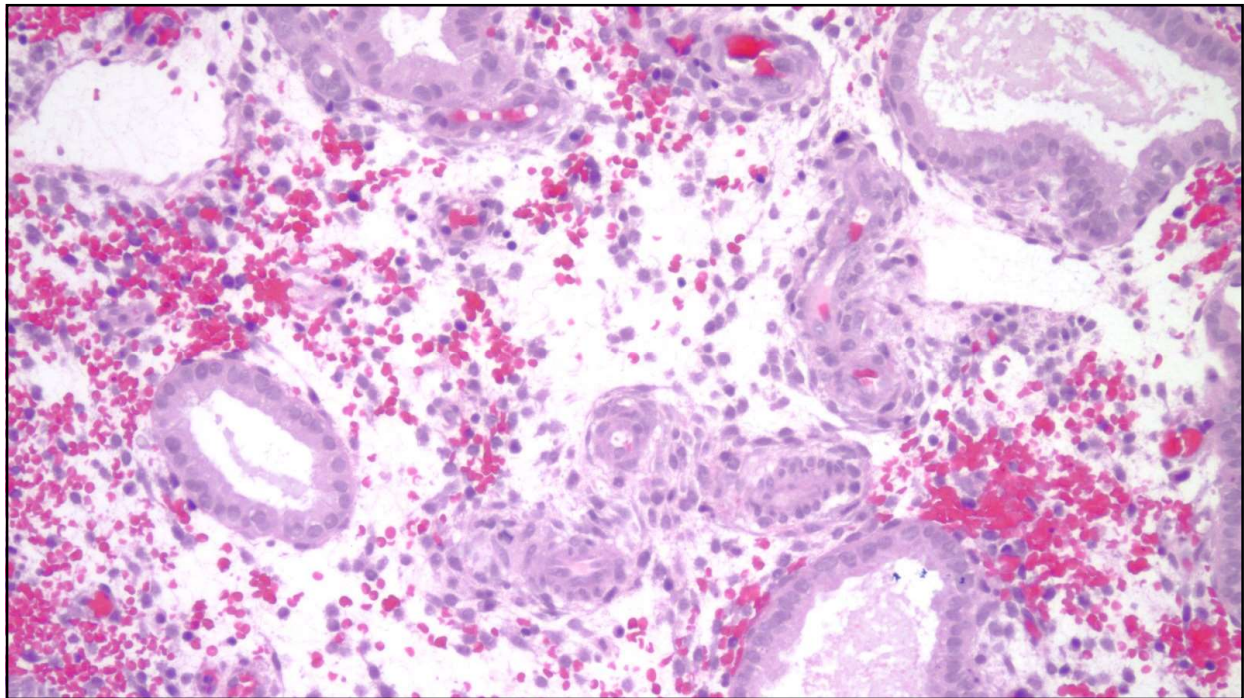
Endometrial Stroma

Spindled	Compact	Edema	Predecidua	Decidua
Menstrual phase	Early/late proliferative	Mid proliferative	Late secretory	Pregnancy
Early proliferative	Early secretory	Mid secretory	OCs	Progestin Rx
Endometritis	Atrophy	Endometritis	HRT	

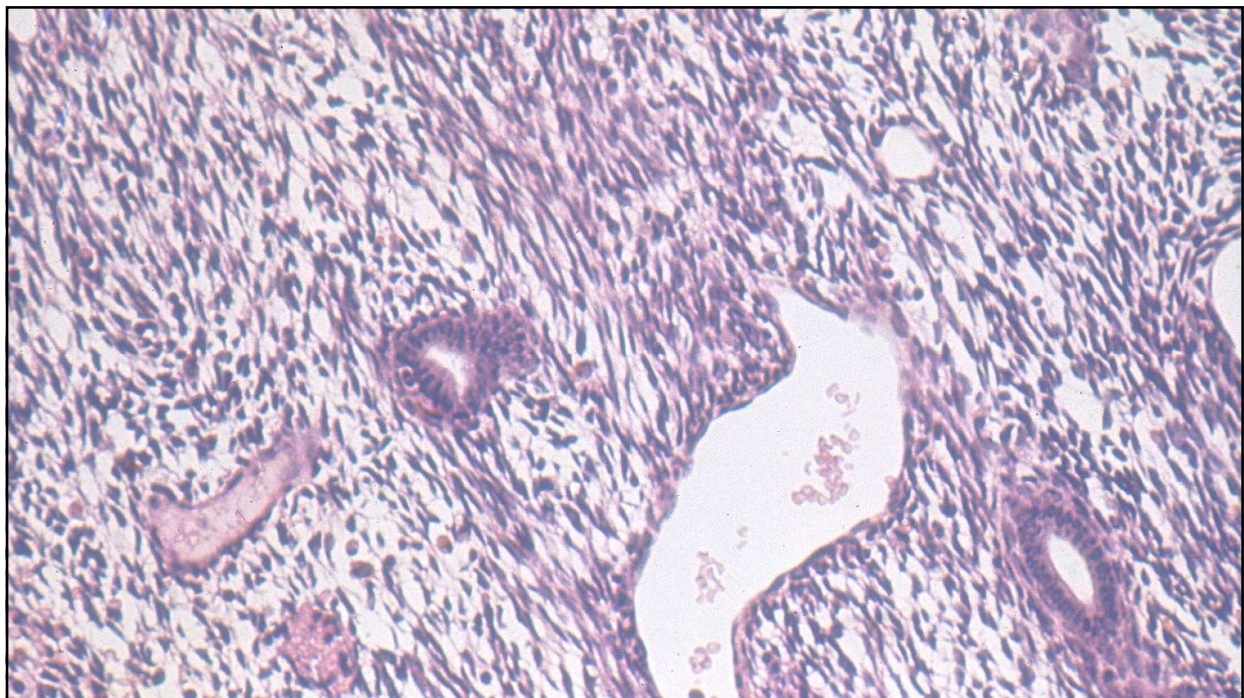
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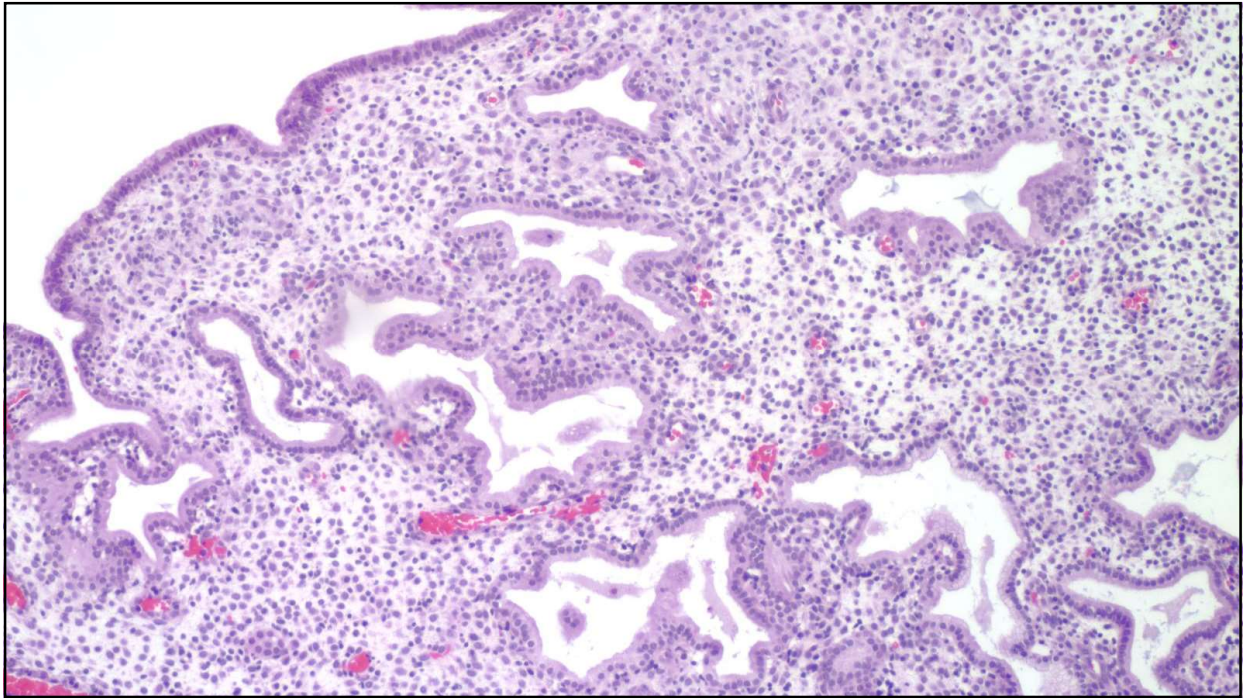
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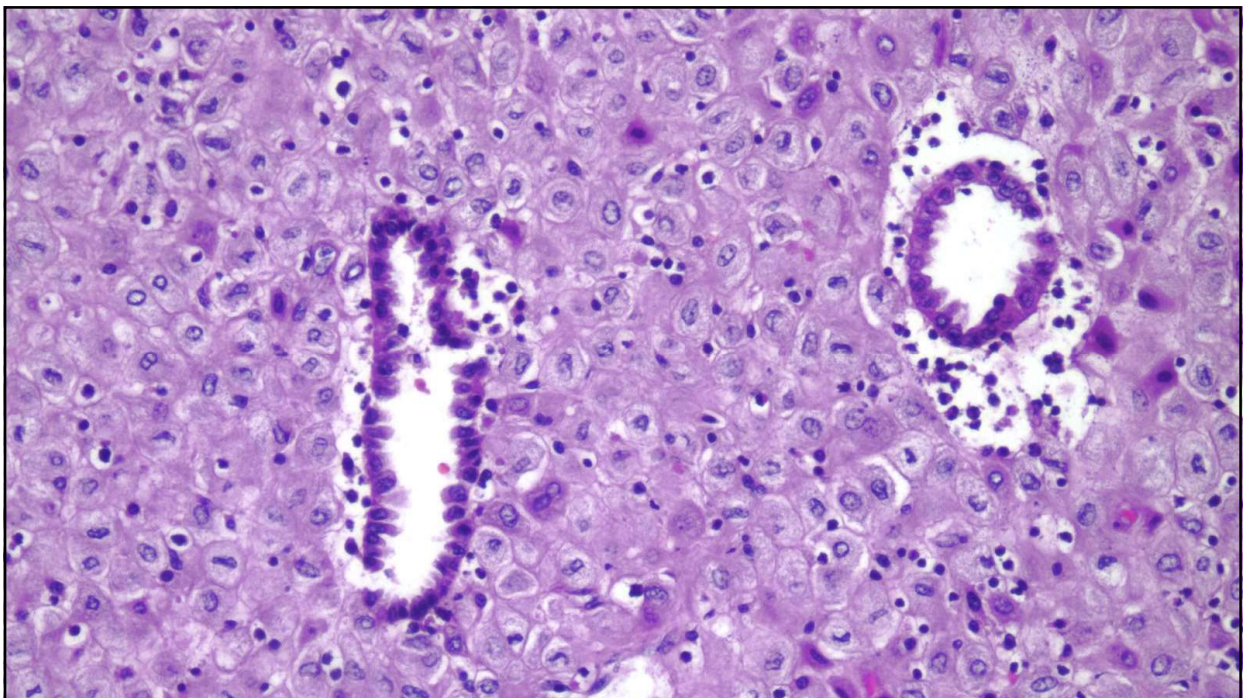
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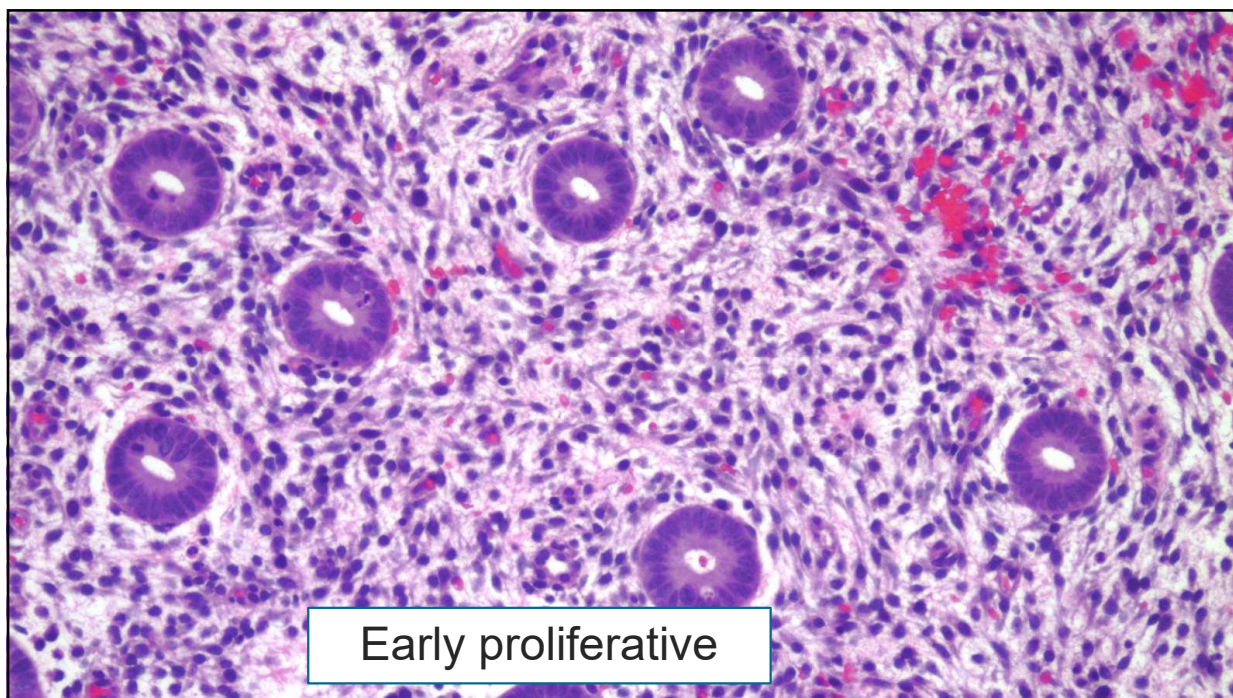
Normal menstrual cycle/physiologic findings

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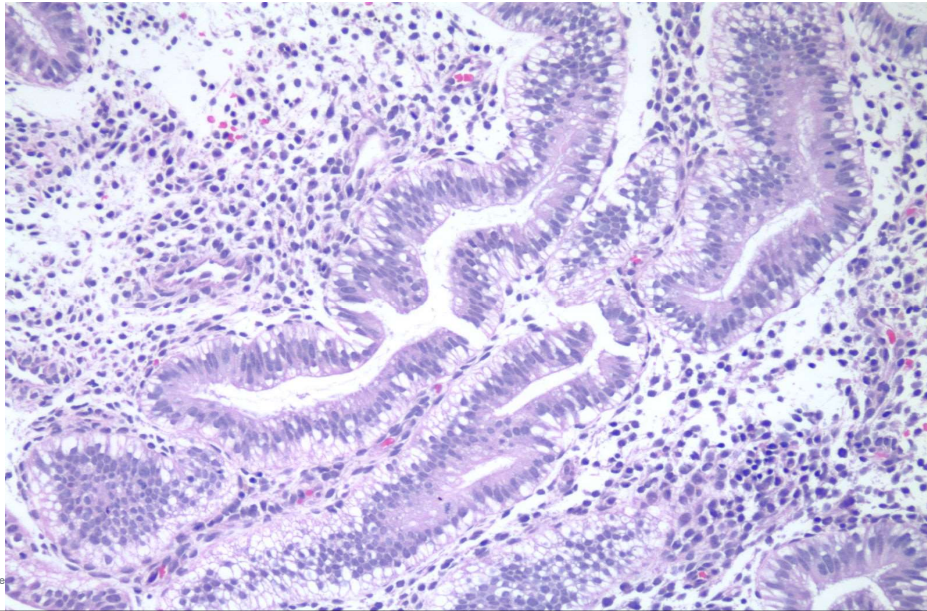
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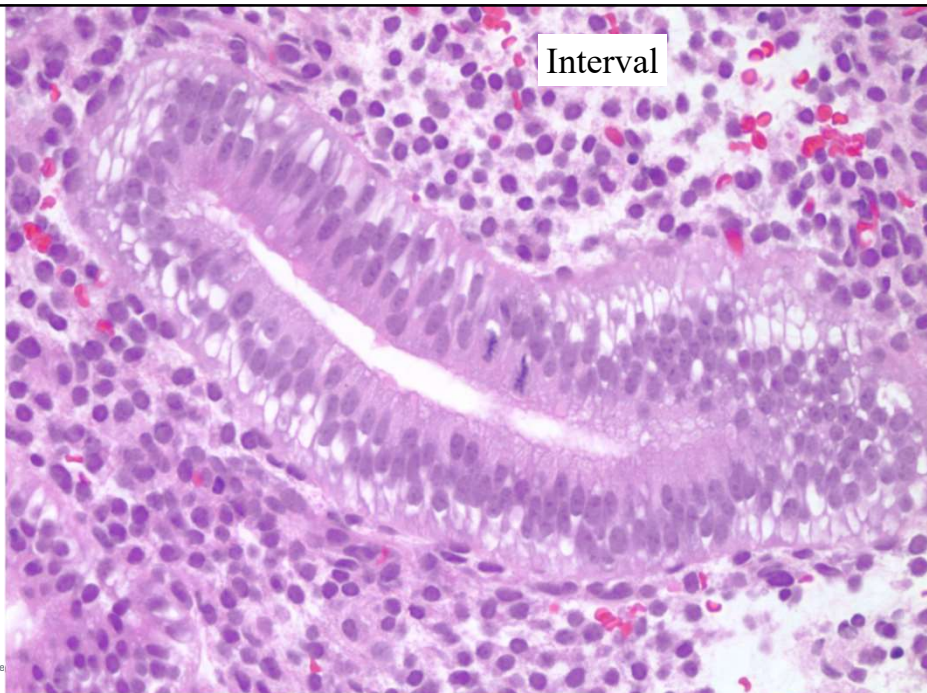
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Interval



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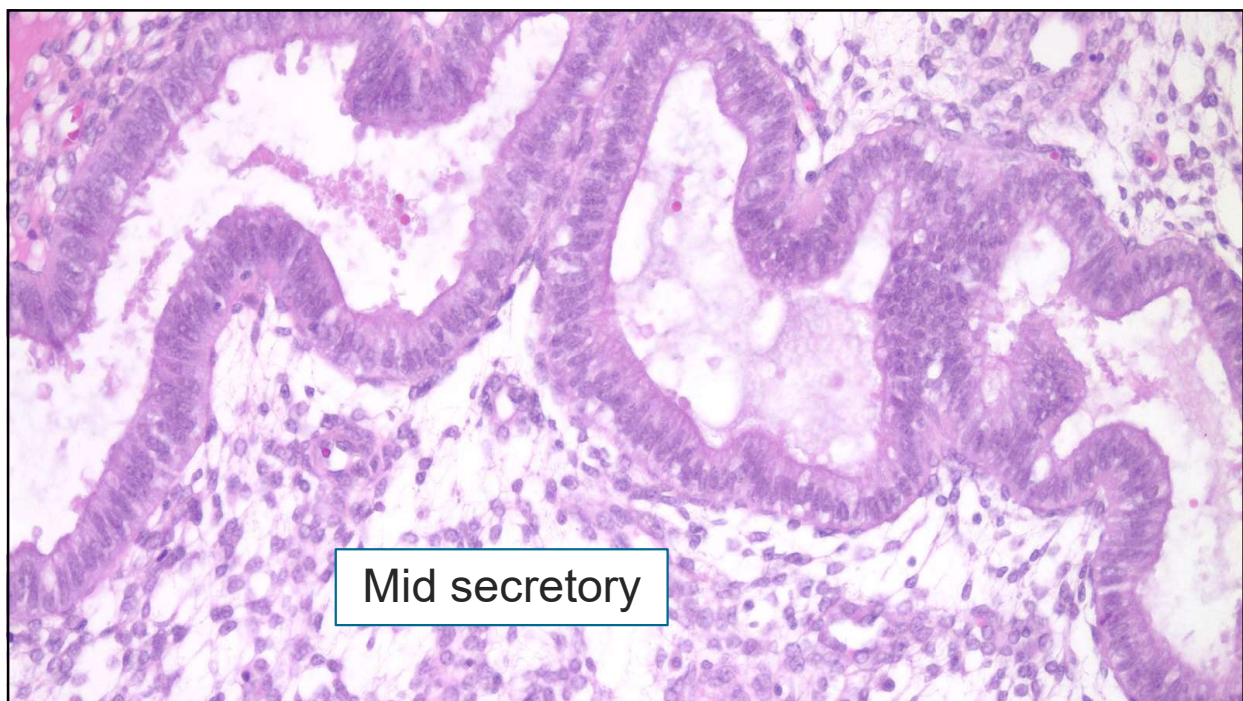
Interval



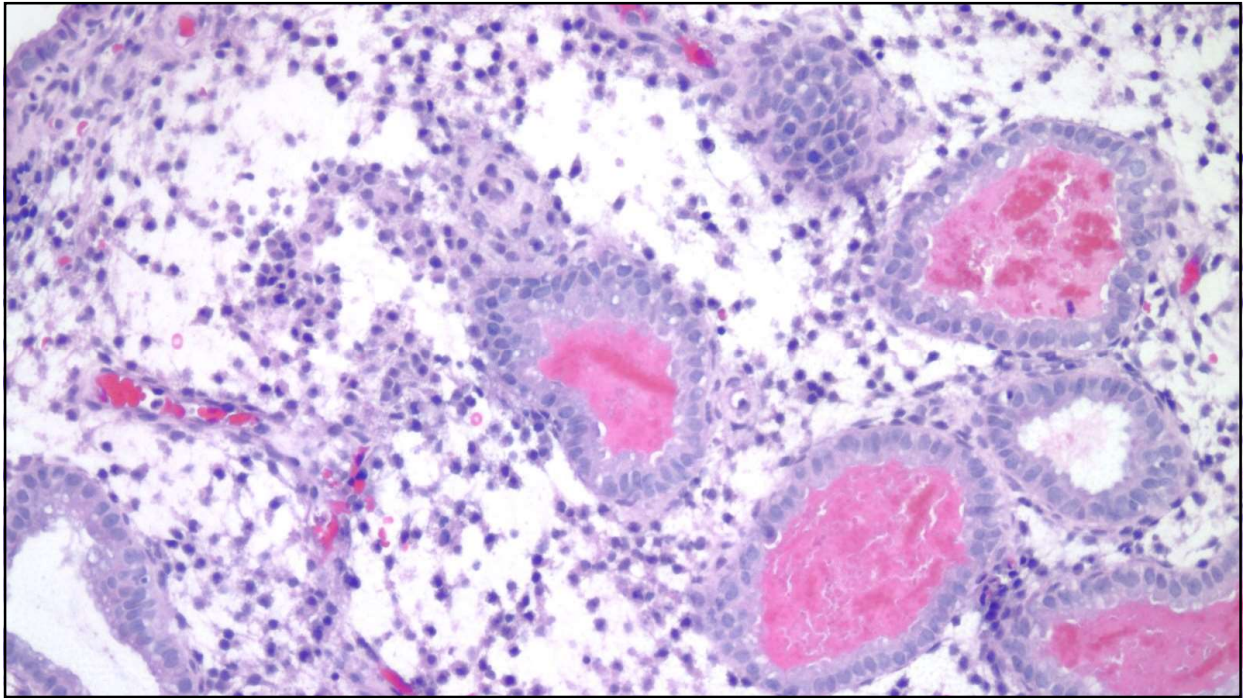
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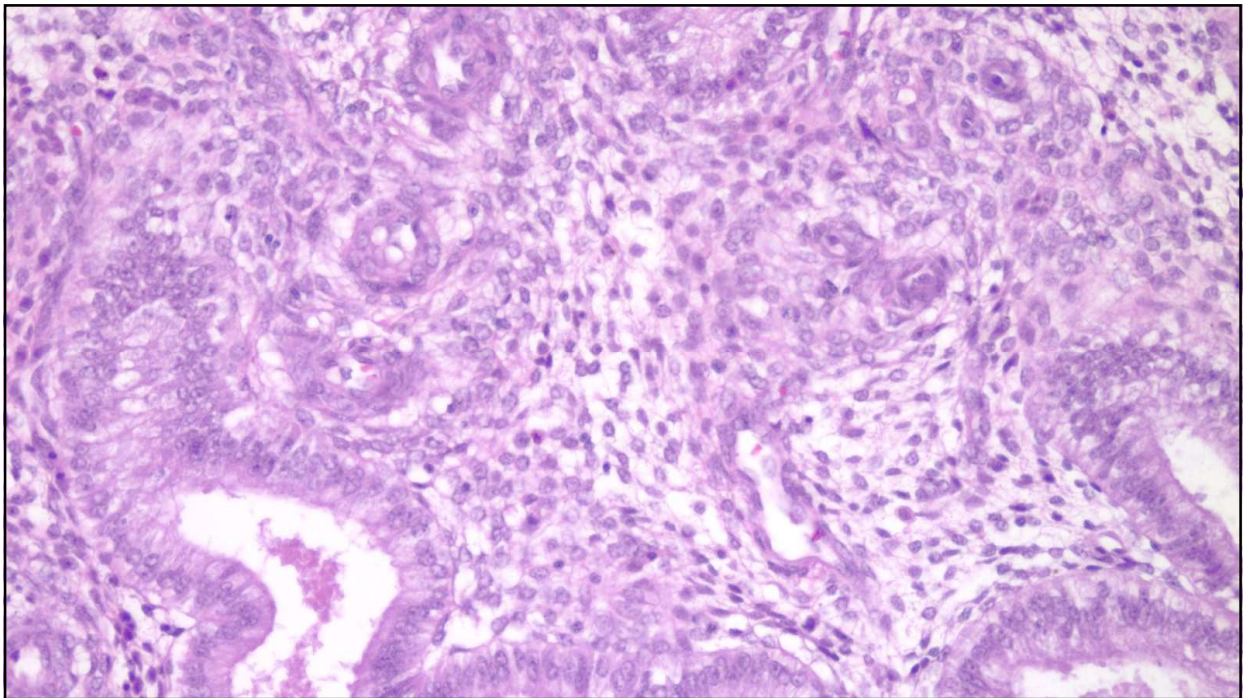
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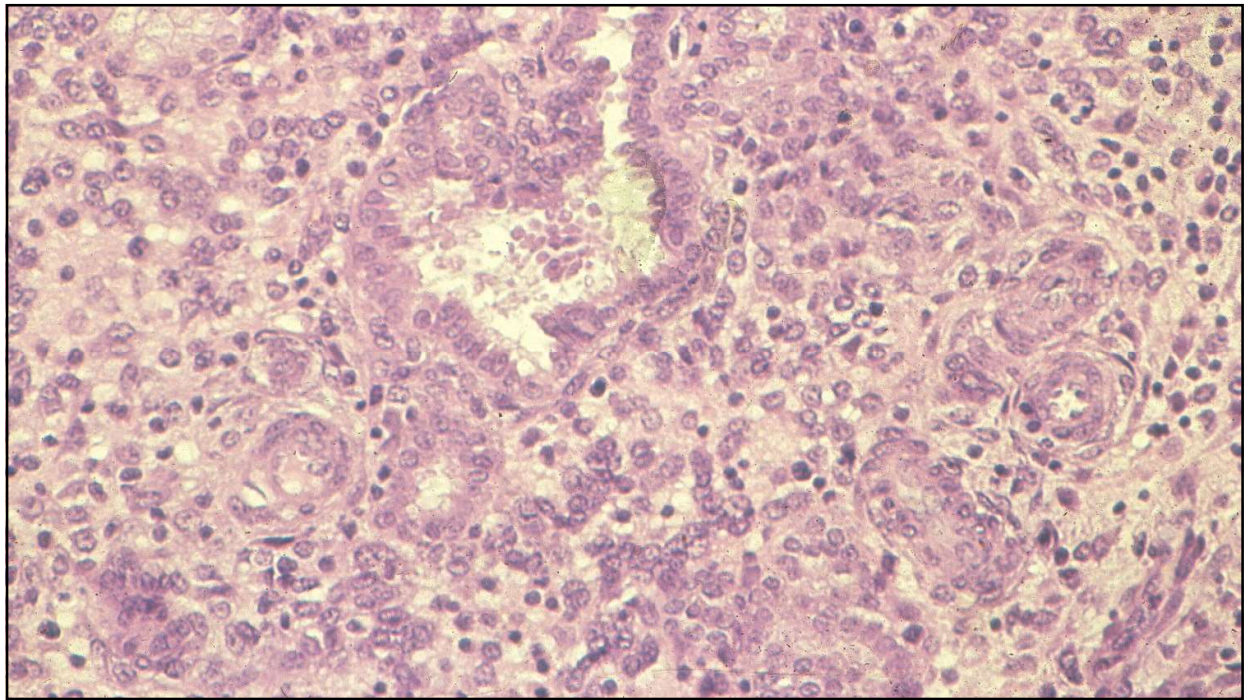
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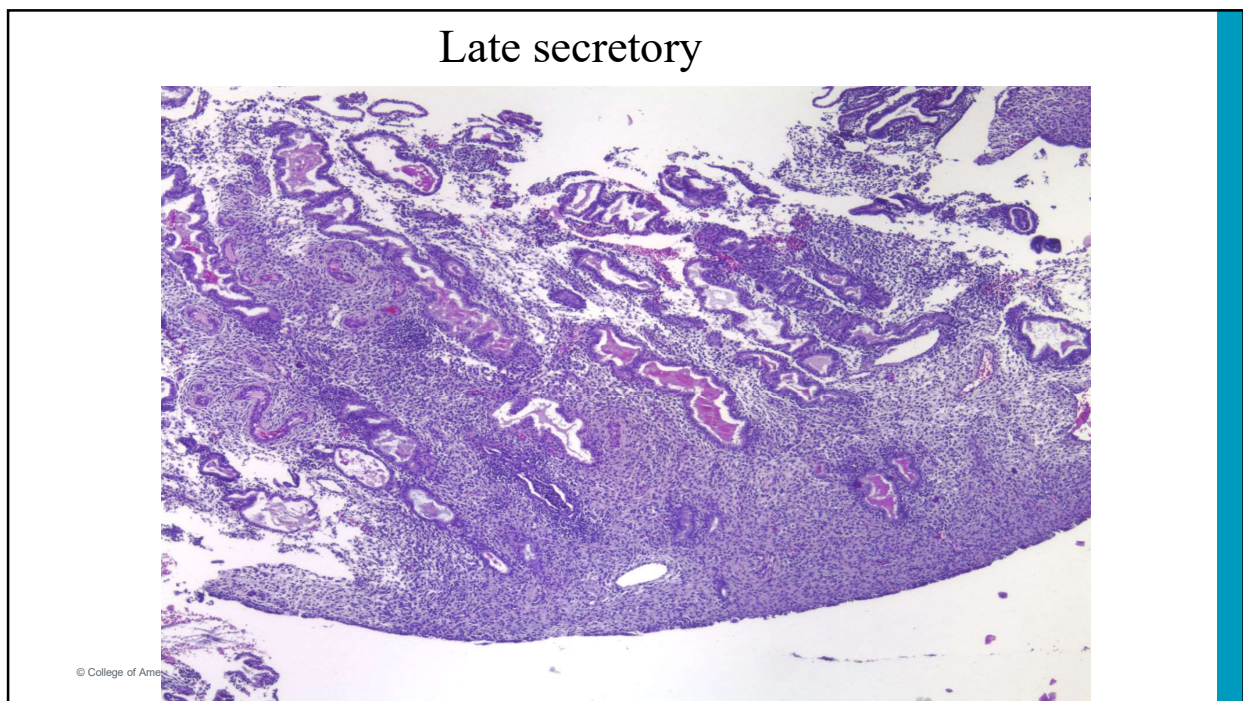
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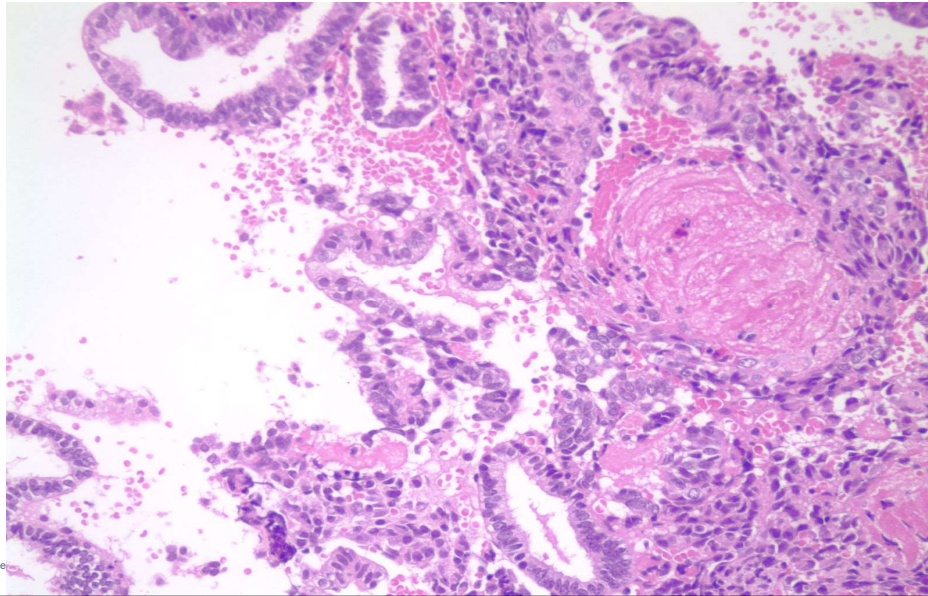


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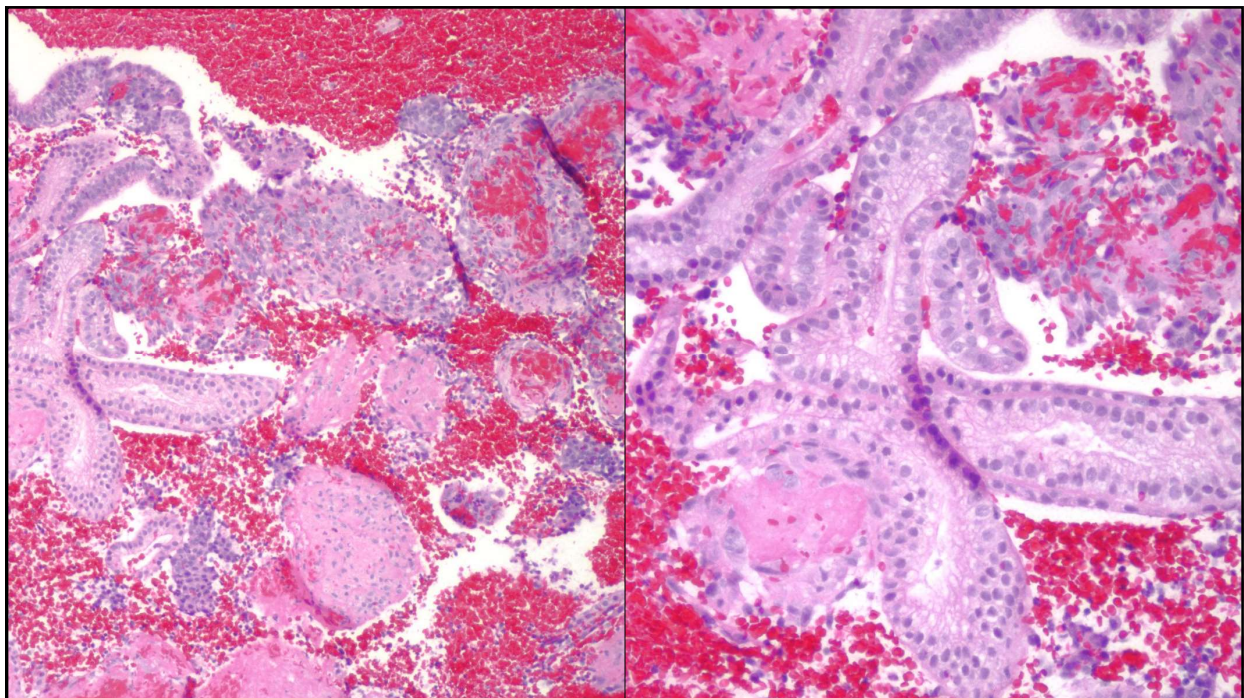


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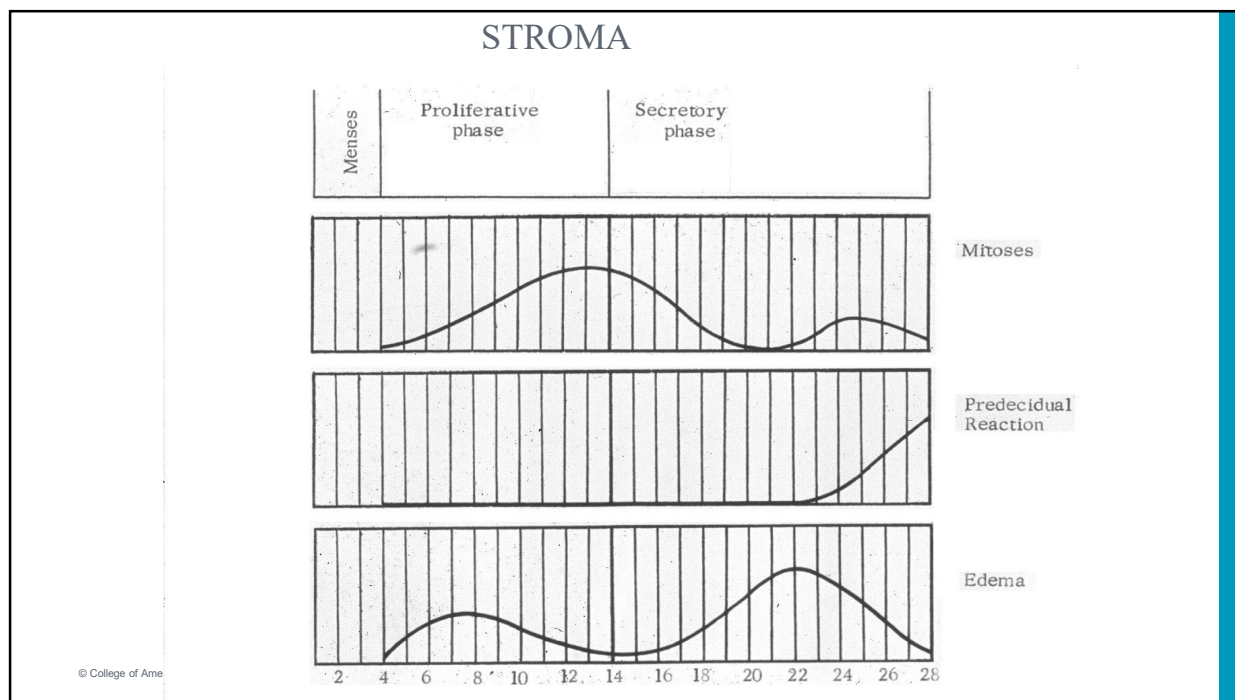
Menstrual



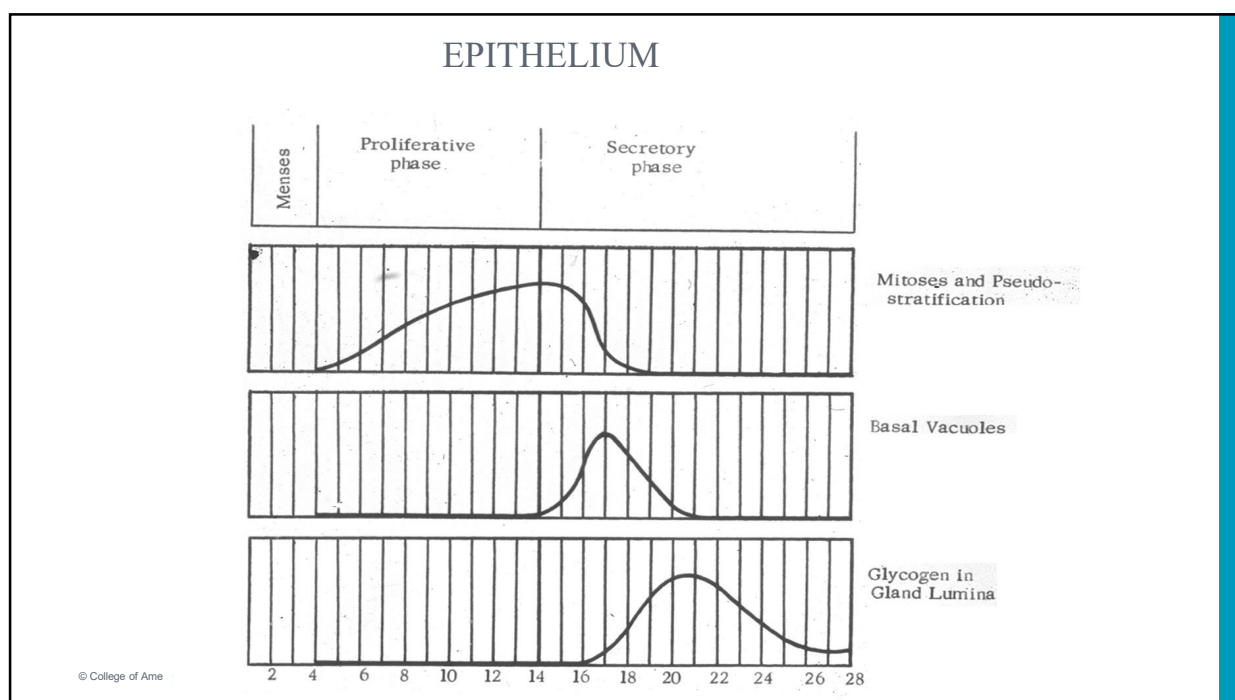
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Dating of endometrium

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Conditions preventing accurate dating

Acute and chronic endometritis

LUS

Polyps

Exogenous hormone effect

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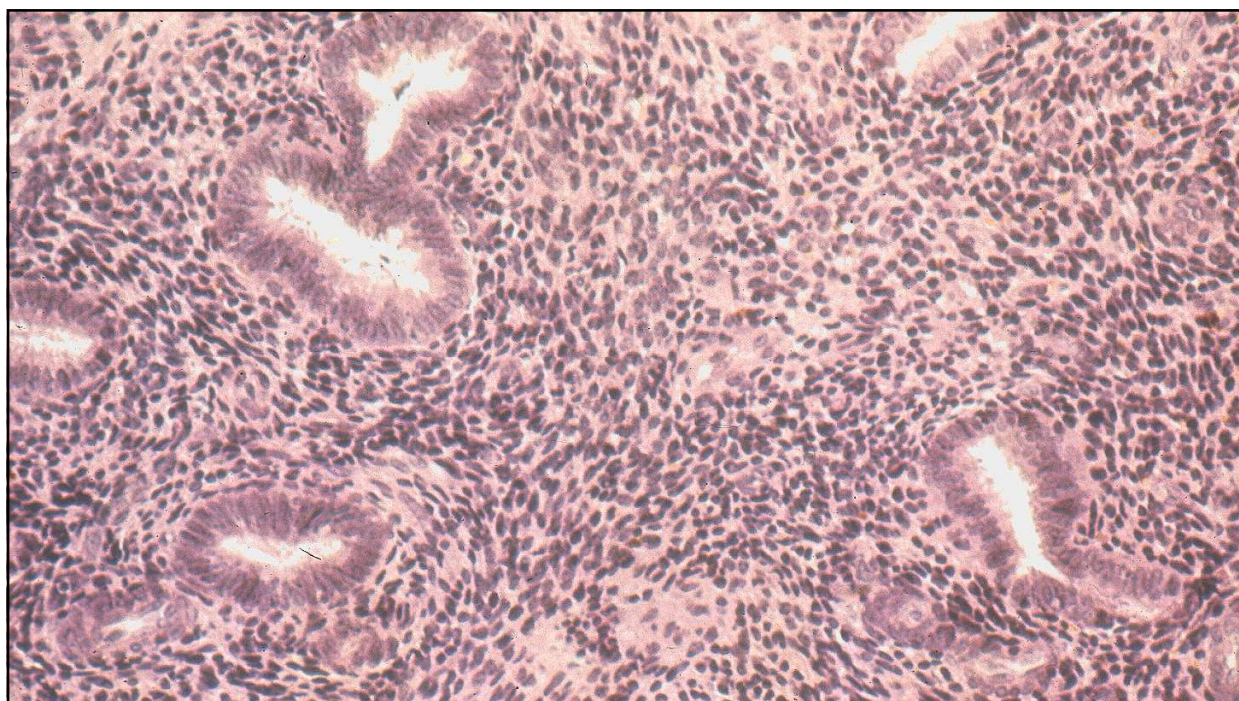
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Physiologically Non-cycling Endometrium

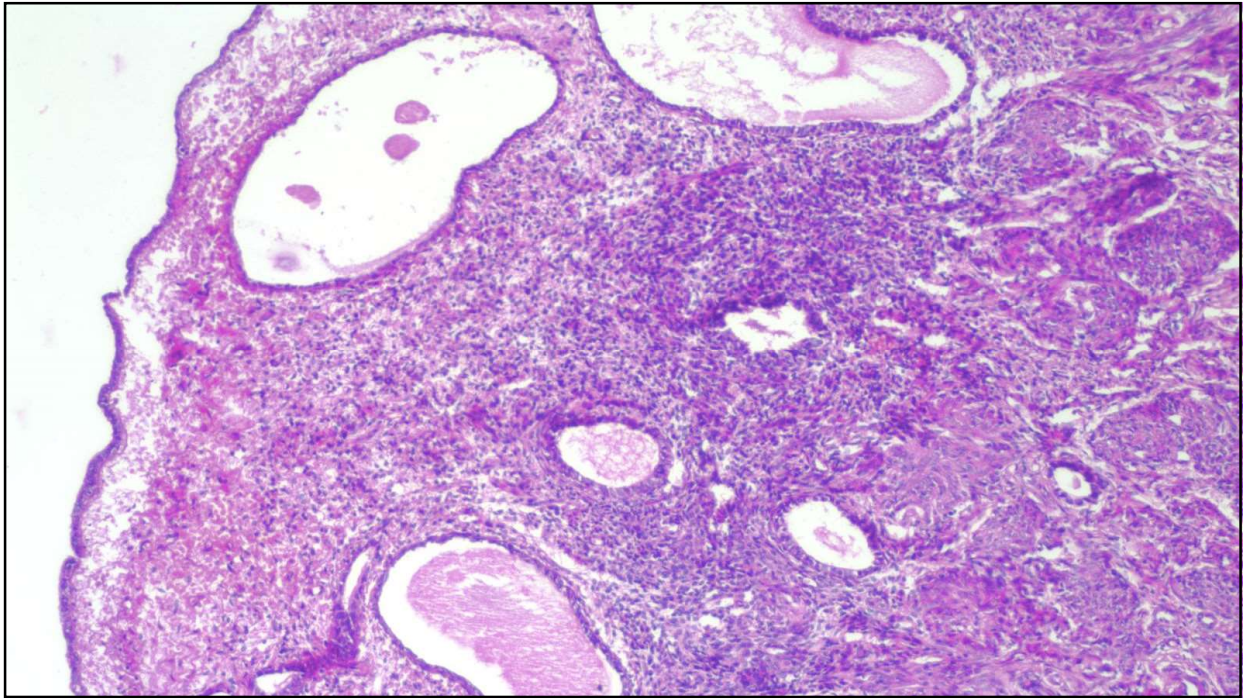
Prepubertal	Postmenopausal	Gestational
<ul style="list-style-type: none">• Inactive	<ul style="list-style-type: none">• Weakly proliferative• Inactive• Atrophy	

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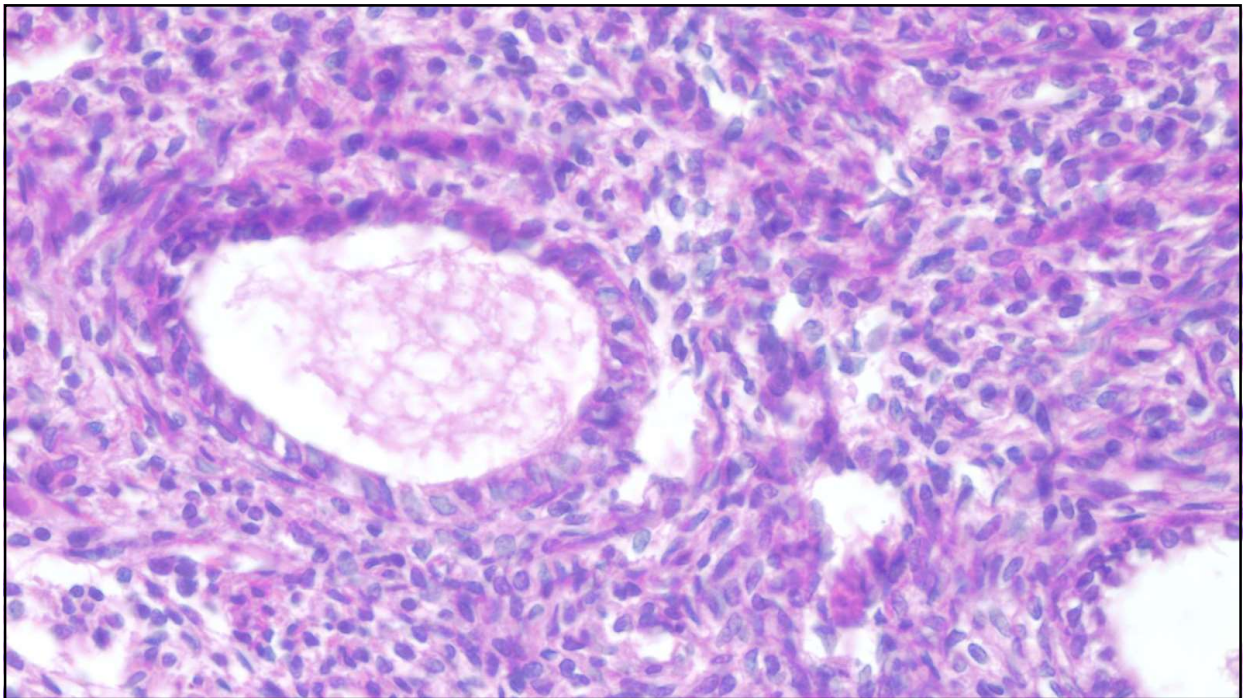
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Selected topics

Infertility work-up

Abnormal uterine bleeding

Exogenous hormone effect

Antineoplastic therapy effect

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Infertility

- ~20% married women
- Almost half caused by hormonal imbalance/ovulatory dysfunction
- Three basic patterns:
 - Amenorrhea
 - Anovulation
 - Ovulatory cycles with deficient luteal or follicular phase
 - Histology is poorly defined, unreliable
- EMBX is useful only to exclude organic pathology
 - Endometritis, polyps, submucosal leiomyomas

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Endometrial dating in infertility work-up

- Does not have the accuracy or the precision necessary for the diagnosis of luteal phase deficiency or to guide the clinical management of women with reproductive failure
- Histological dating does not discriminate between women of fertile and infertile couples, does not predict outcome
- No relation to out-of-phase findings

Fertil Steril. 81:1333;2004

Fertil Steril.82:1264;2004

Fertil Steril.86:1344; 2006

Int J Gynecol Pathol 21:231; 2002

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Abnormal uterine bleeding

Terms:

- metrorrhagia (intermenstrual/irregular bleeding)
- menorrhagia (heavy or long menses)
- menometrorrhagia

Causes:

- Complications of pregnancy
- Organic lesions (leiomyoma, adenomyosis, polyps, endometritis, endometrial hyperplasia, carcinoma)
- Dysfunctional uterine bleeding – no organic lesion
- Postmenopausal bleeding

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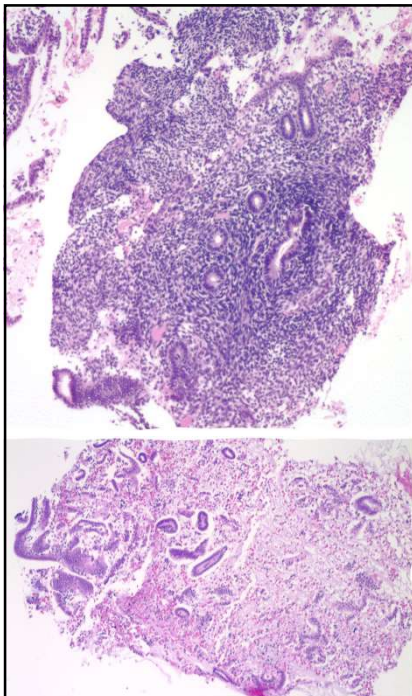
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Abnormal uterine bleeding

- Polyp
- Endometritis (acute, chronic)
- Leiomyoma (submucosal)
- IUD
- Hormonal therapy
- Atrophy
- Hyperplasia, carcinoma

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Atrophy: What is sufficient for Dx?

- Pre/perimenopausal woman
 - At least one intact fragment with stroma
- Postmenopausal woman/atrophic endometrium
 - At least 5 strips of atrophic glands

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Follow-up of insufficient EMBX: which patients are more likely to develop/harbor cancer?

- **>60 yo**
- **Not on HRT**
- **Recurrent bleeding**
- **Abnormal hysteroscopy**
- **> 4mm endometrial stripe**

Bachmann et al, Acta Obstet Gynecol Scand. 2003;82:564

Visser et al, Acta Obstet Gynecol Scand. 2016 95:1418-1424

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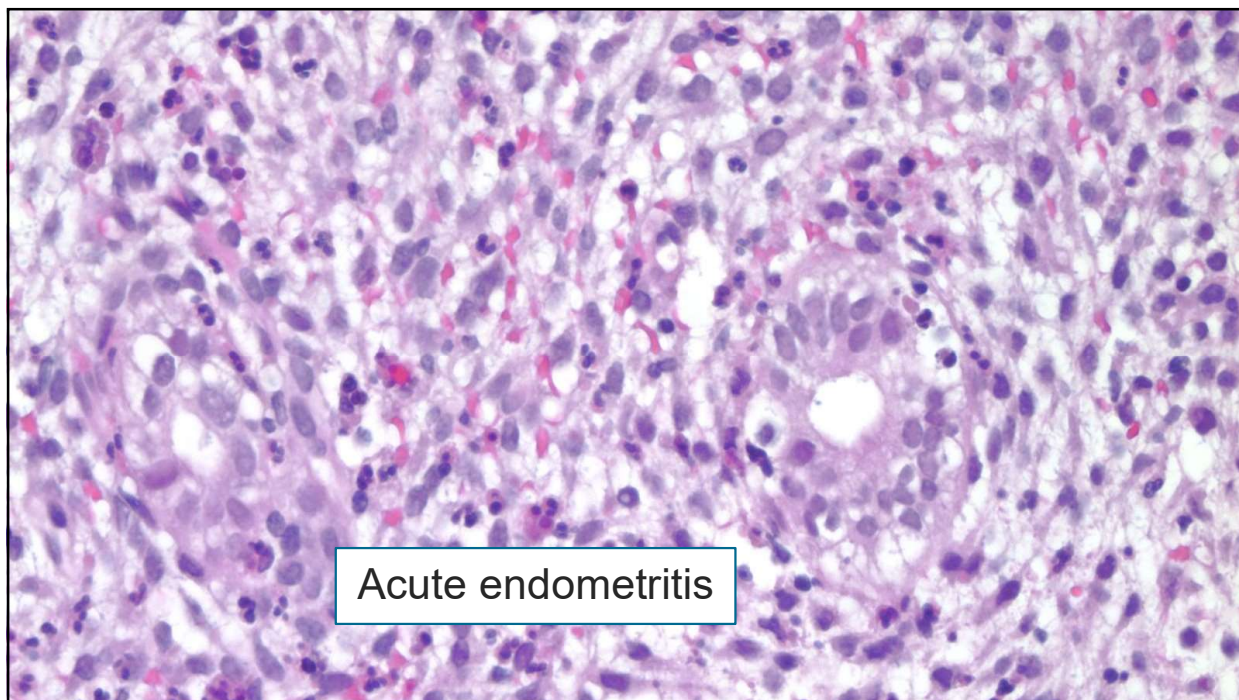
Organic lesions: Endometritis

Acute (bacterial) – post delivery/miscarriage/abortion; caused by retained products of conception

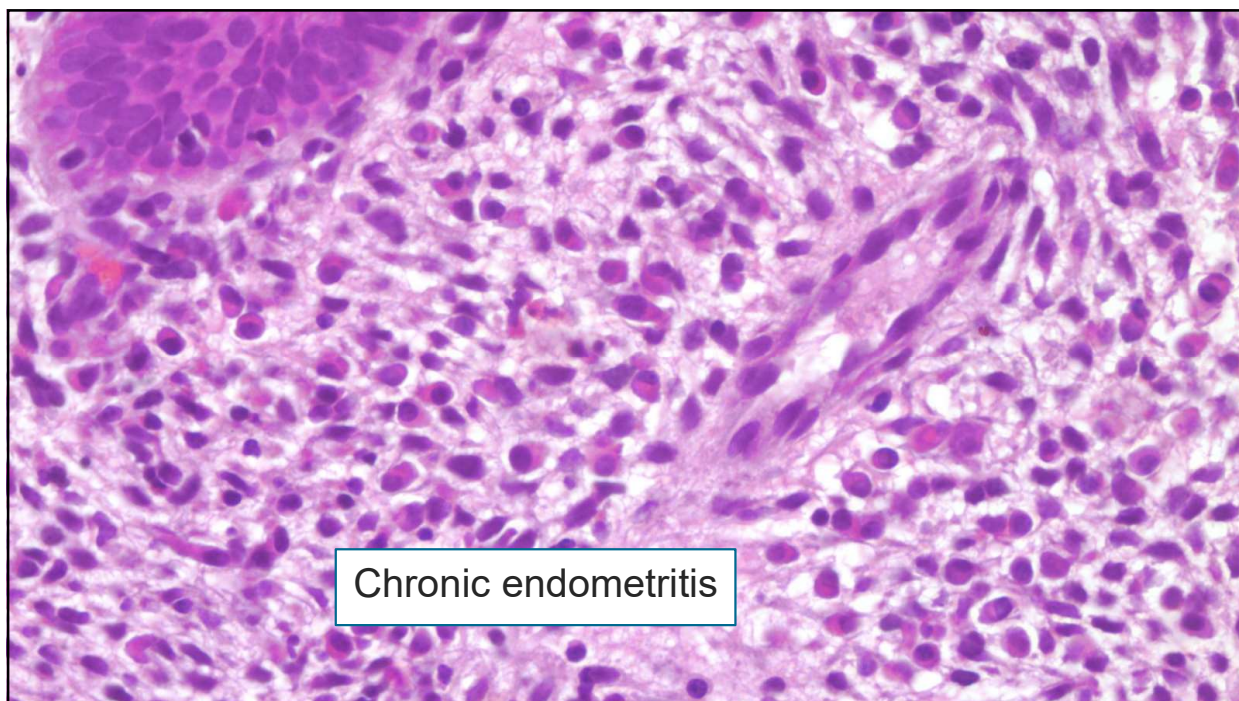
Chronic endometritis:

- Pelvic inflammatory disease (PID), e.g. *Chlamydia*
- IUD
- tuberculosis (from TB salpingitis or hematogenous spread)

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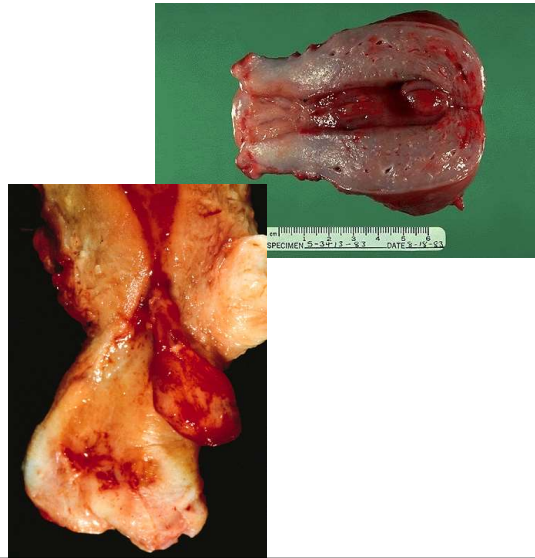
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Organic lesions: Endometrial polyp

- Benign, exophytic
- Stroma is neoplastic, glands are not
- May cause bleeding
- No premalignant potential
- Associated with Tamoxifen Rx



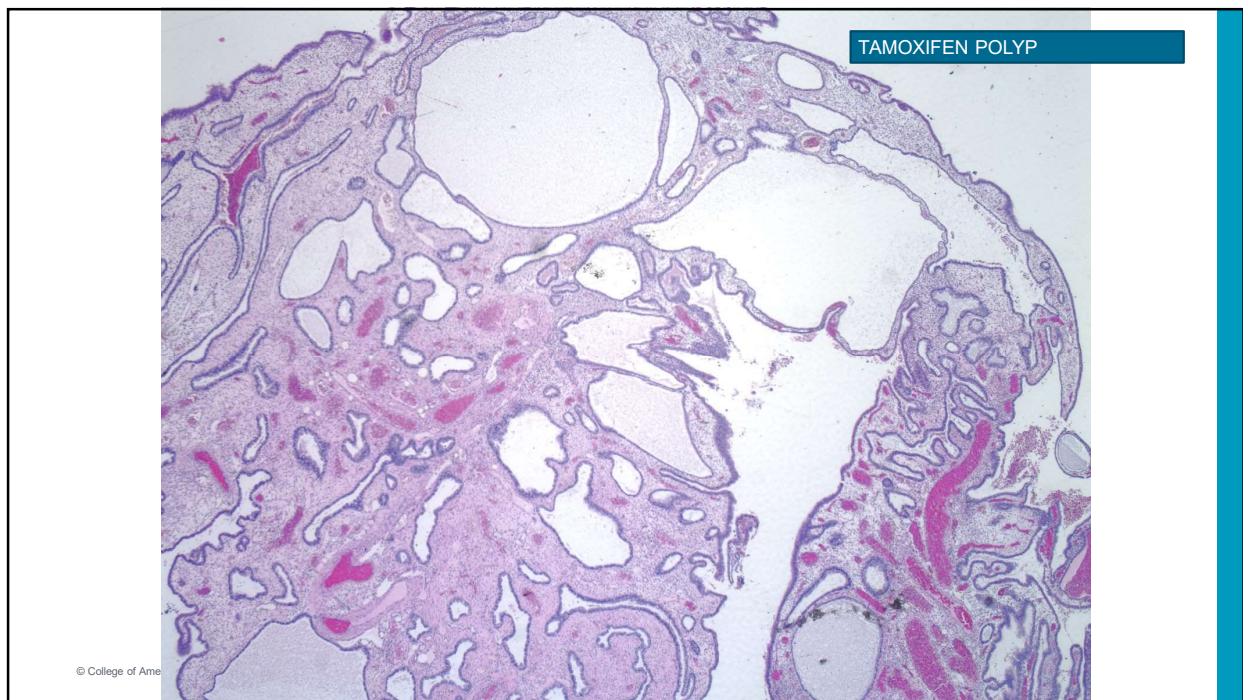
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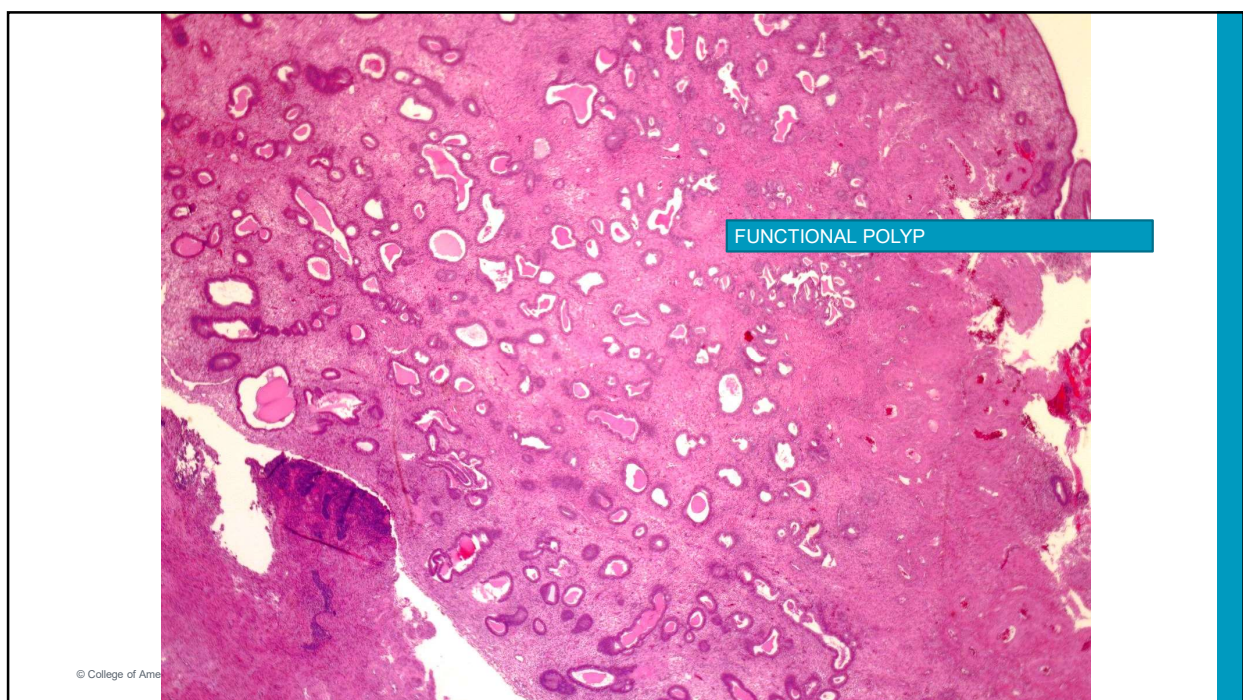


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Dysfunctional Uterine Bleeding

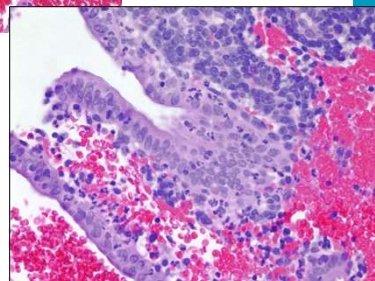
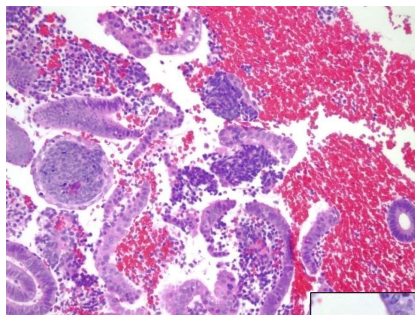
- Abnormal cycle length or excessive bleeding
- No primary uterine abnormalities or systemic disease
- Most – anovulation; or abnormal ovulatory cycles

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Histology of Dysfunctional Uterine Bleeding

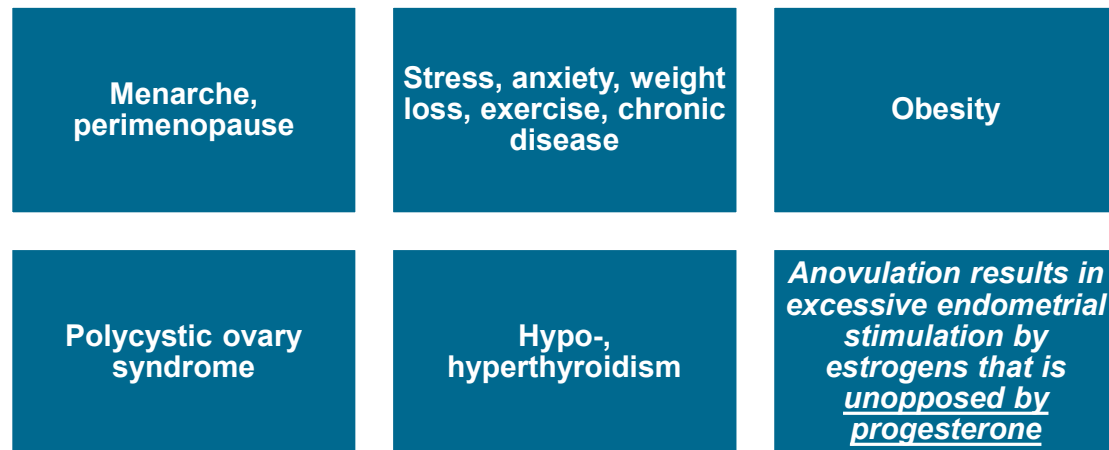
- **Non-menstrual bleeding pattern**
 - Anovulatory pattern (disordered proliferative) = estrogen breakthrough bleeding
 - Perimenopausal, menopausal pts
 - Weakly proliferative/inactive with bleeding: estrogen withdrawal bleeding
 - Menopausal pts
 - Hormonal treatment



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Anovulation



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Endogenous Estrogen Excess

- **Perimenopausal women**
 - anovulatory cycles - repeated
 - polycystic ovary disease (Stein-Leventhal syndrome) and/or obesity
- **Postmenopausal women with predominant estrogen stimulation (obesity, unopposed HRT)**
- **Pre- or postmenopausal women with ovarian hyperthecosis or ovarian stromal hyperplasia, or estrogen-producing tumor**

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Endogenous Estrogen Excess

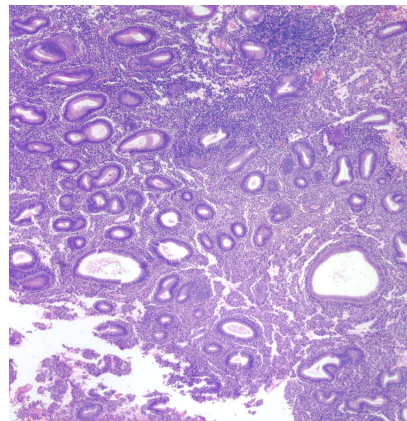
- **Proliferative/weakly proliferative or “Disordered” proliferative**
 - Tubal metaplasia common
 - Glandular cell apoptosis
 - Stromal breakdown, fibrin thrombi: focal bleeding pattern
- **Eventually, some (minority) pts develop hyperplasia**

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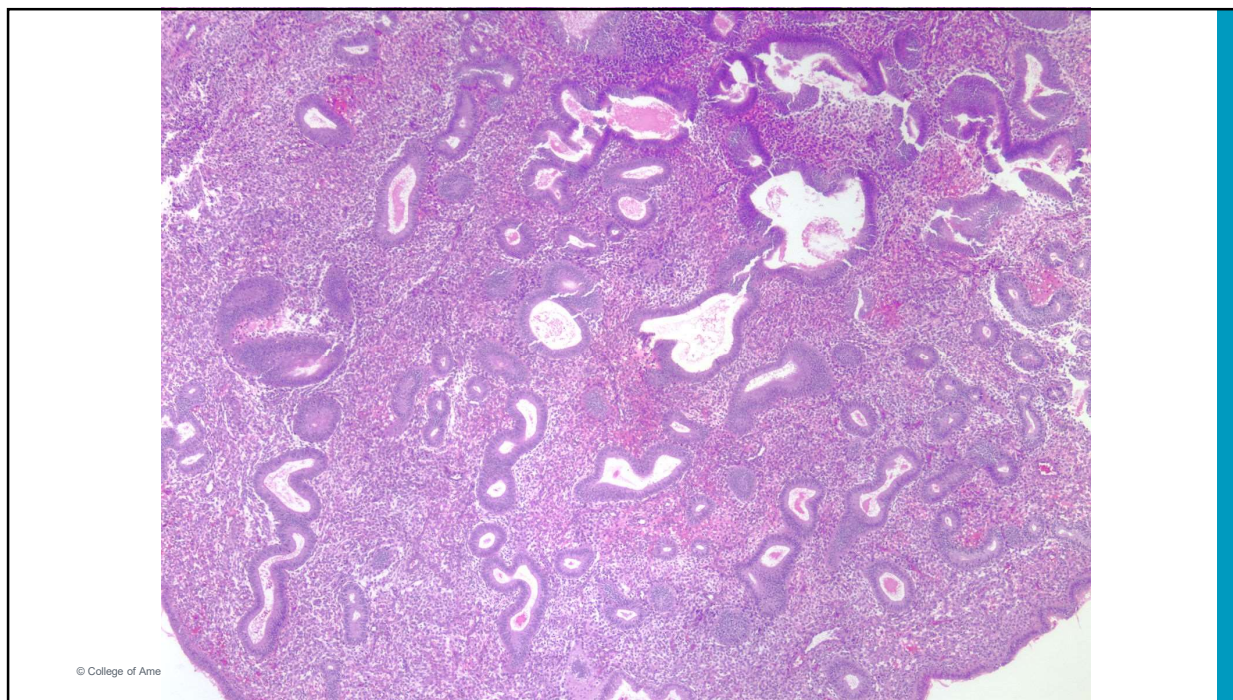
“Disordered” Proliferative Endometrium

- **Thicker endometrium**
- **Diffuse but nonuniform development – “Regularly irregular”**
- **Admixture of straight, coiled and branching glands**
- **Focally dilated glands/cysts**
- **Tubal metaplasia**
- **Apoptosis**

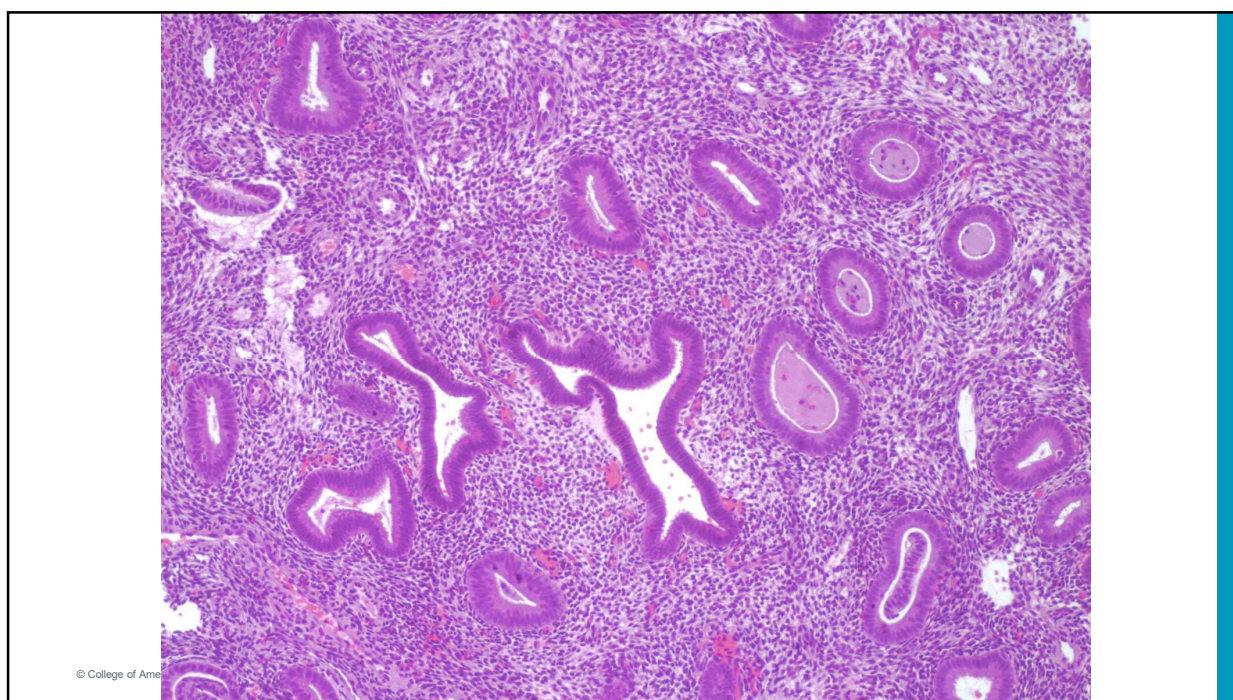


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Exogenous hormone effect: oral contraceptives

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Oral Contraceptives

- **Most – combination of estrogen and progesterone in small doses**
 - Mono-, bi-, triphasic (alterations in progestin dose)
 - Inhibition of gonadotropin secretion; no ovulation, no dominant follicle selection
- **Some (Micronor, Ovrette) – only progestins (“minipill”)**
 - Ovulation occurs; thick cervical mucus and atrophic endometrium

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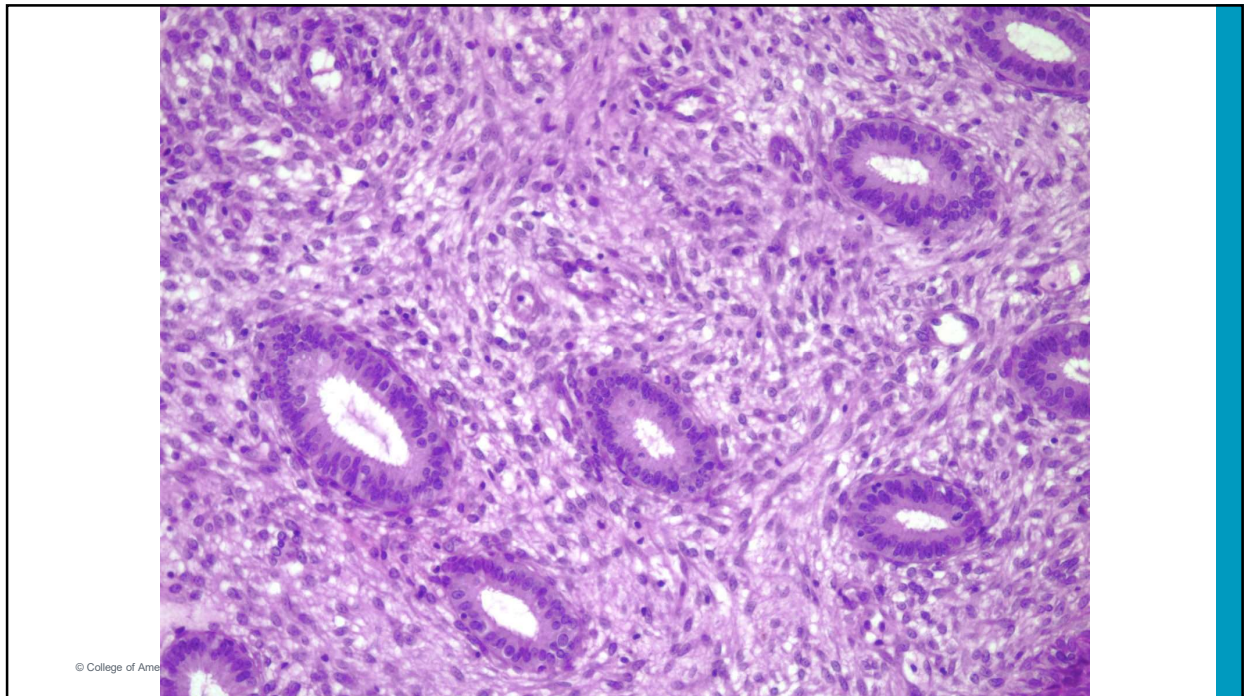
Histology of OCs

- **Combination agents:**

- Gland:stromal ratio <1:1
- Glands arrested in early proliferative phase, occasional vacuoles or dense secretions
- Some glands dilated, resembling vascular channels, with flat epithelium
- Stromal decidual change or edema; occasional PMNs
- Spiral arteries absent; dilated thin-walled vessels, some thrombosed

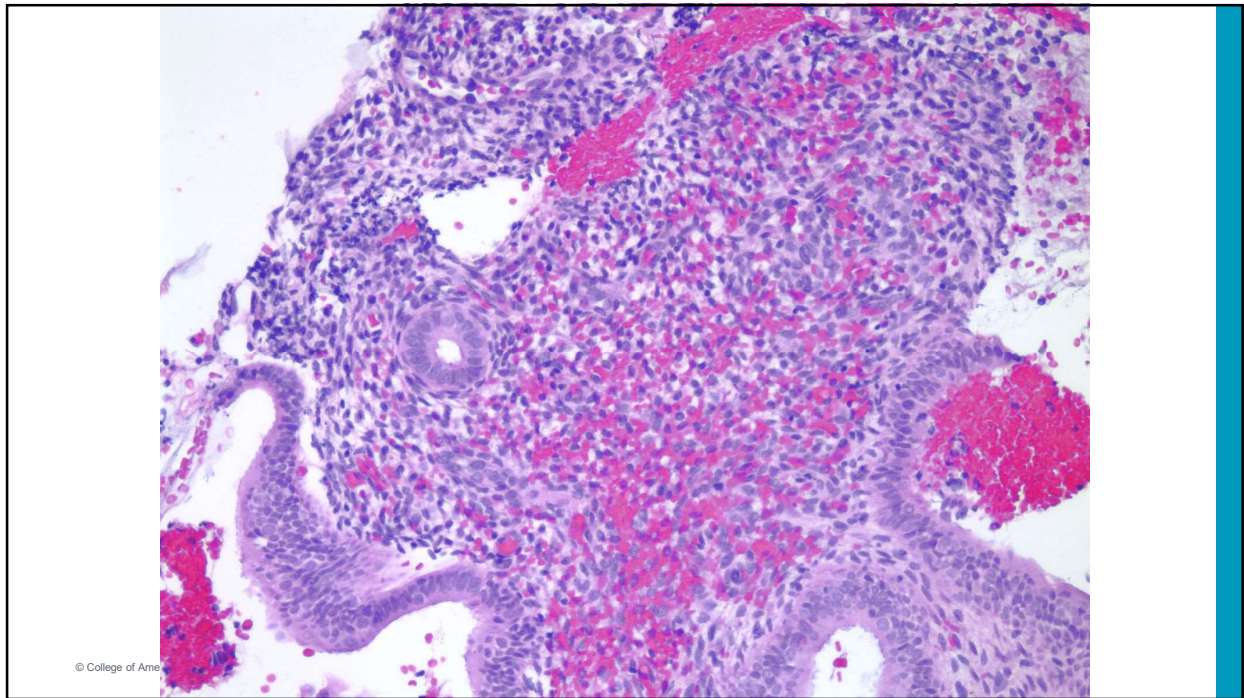
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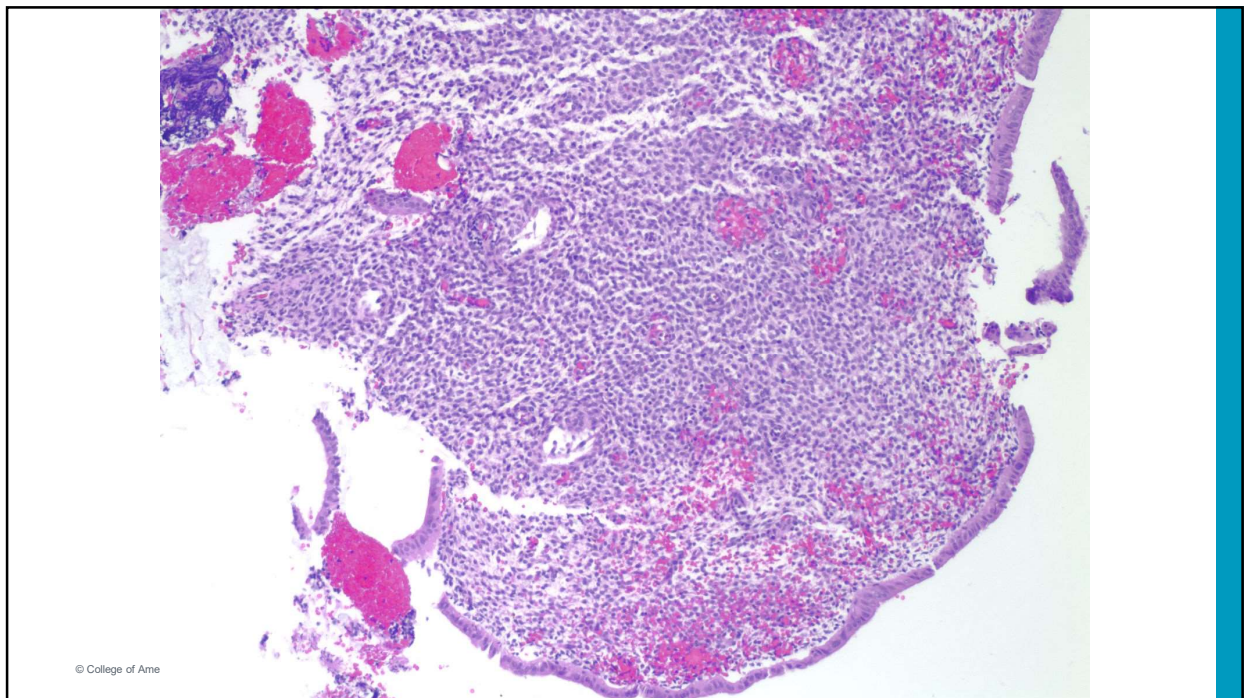


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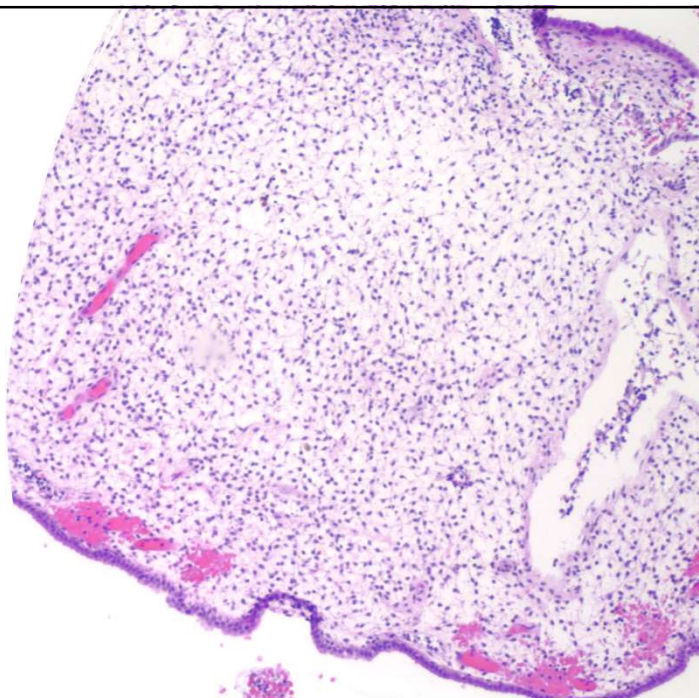


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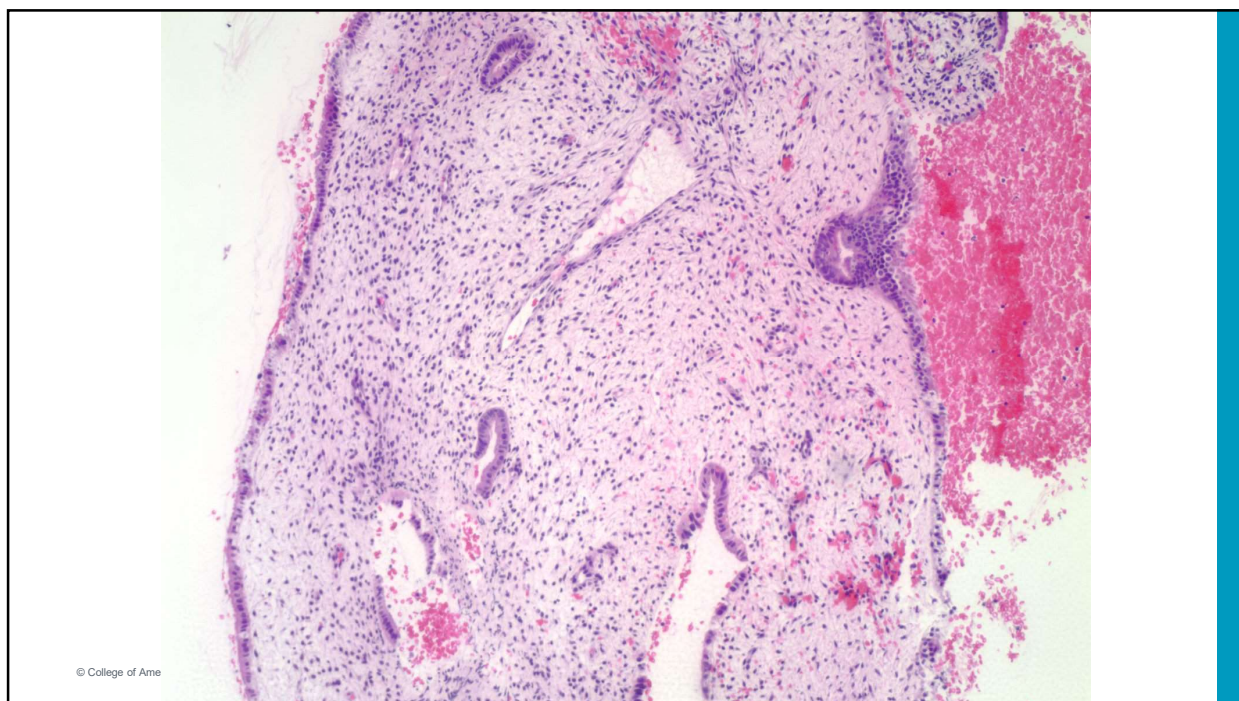
Histology of OCs

- **Progestin-only agents:**
 - Greater atrophy
 - Gland-stromal ratio lower
 - Breakthrough bleeding common

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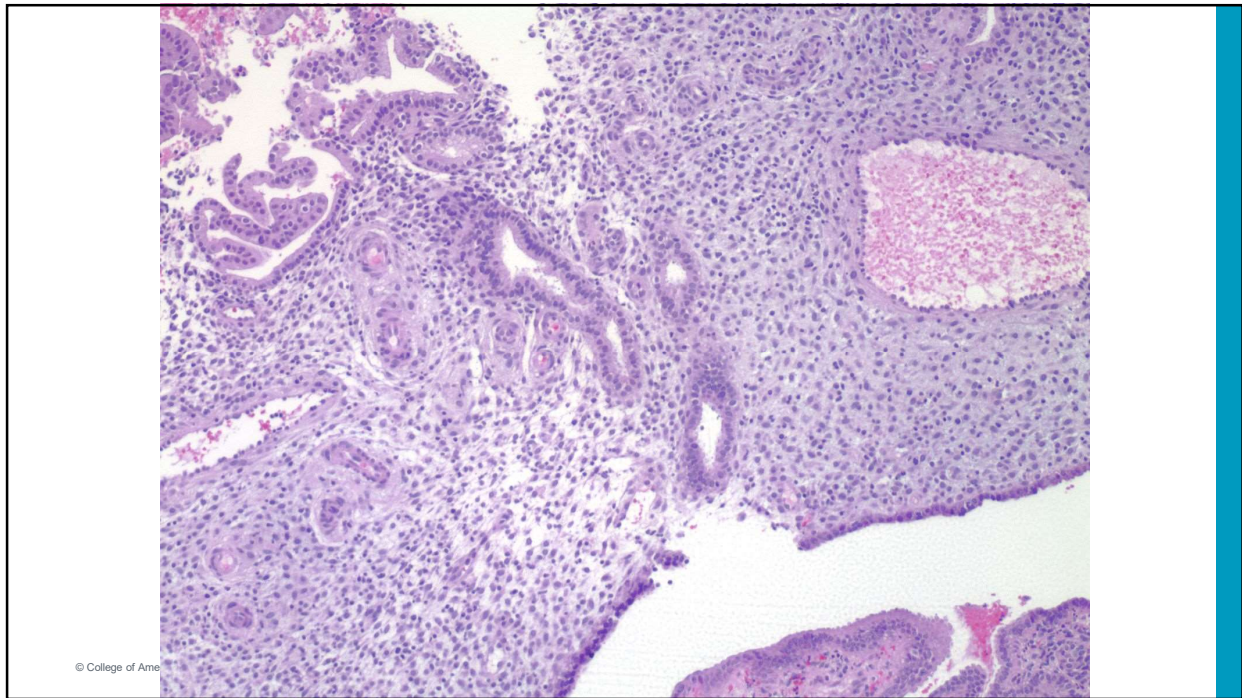


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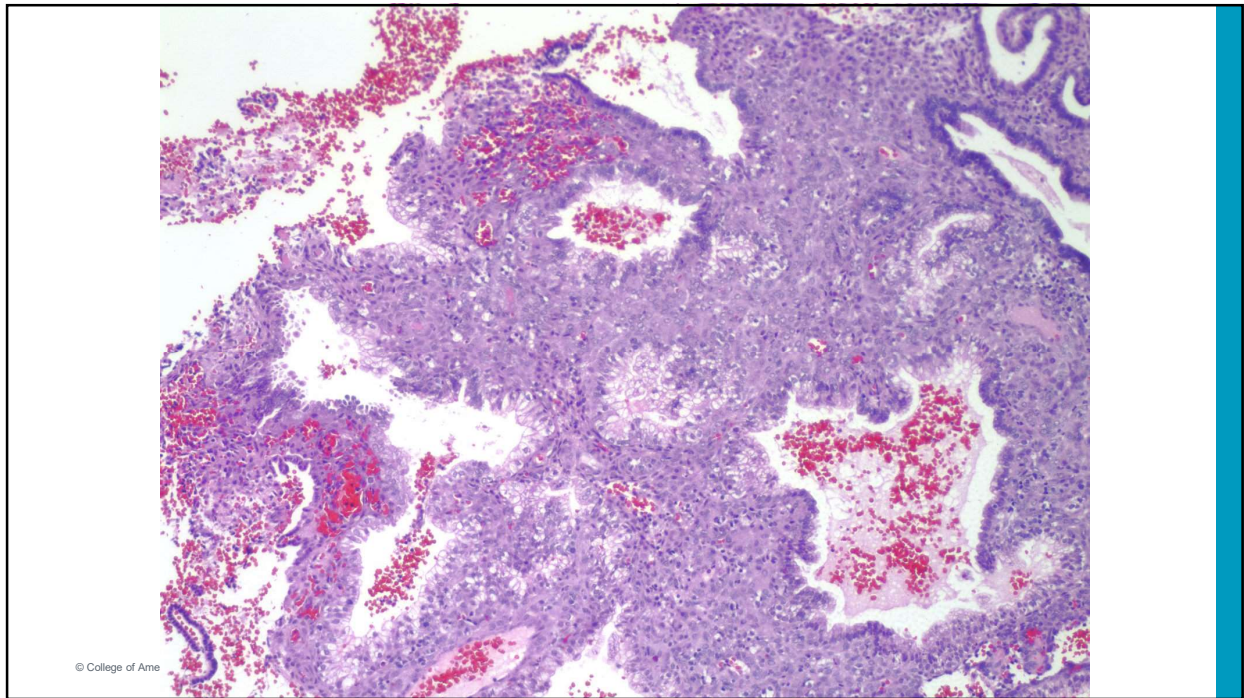
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Long-Acting Contraceptives

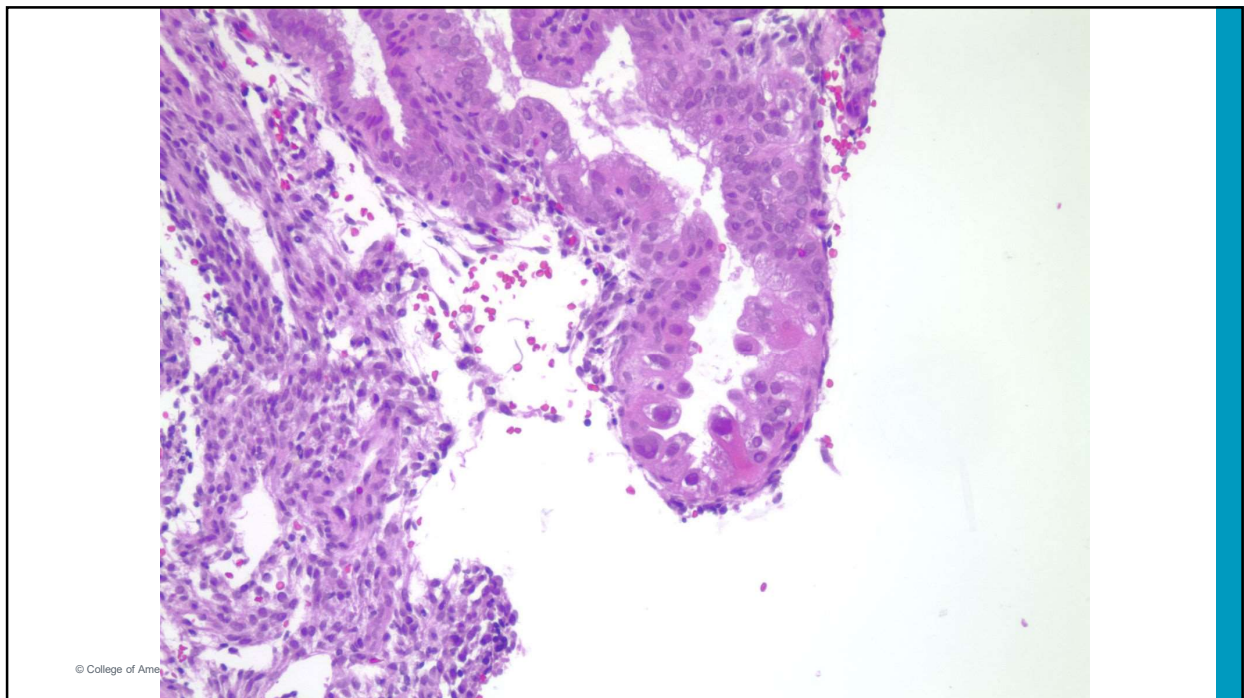
- **Medroxyprogesterone acetate (DepoProvera)**
 - Intramuscular q3 months
 - High levels of progestins
 - Prevents LH surge and ovulation, and implantation
 - Hypersecretory → small glands in decidualized stroma → atrophy
- **Norplant**
 - Sylastic tubes with levonorgestrel in subQ – 3-5 years
 - Similar to progestin-only OCs

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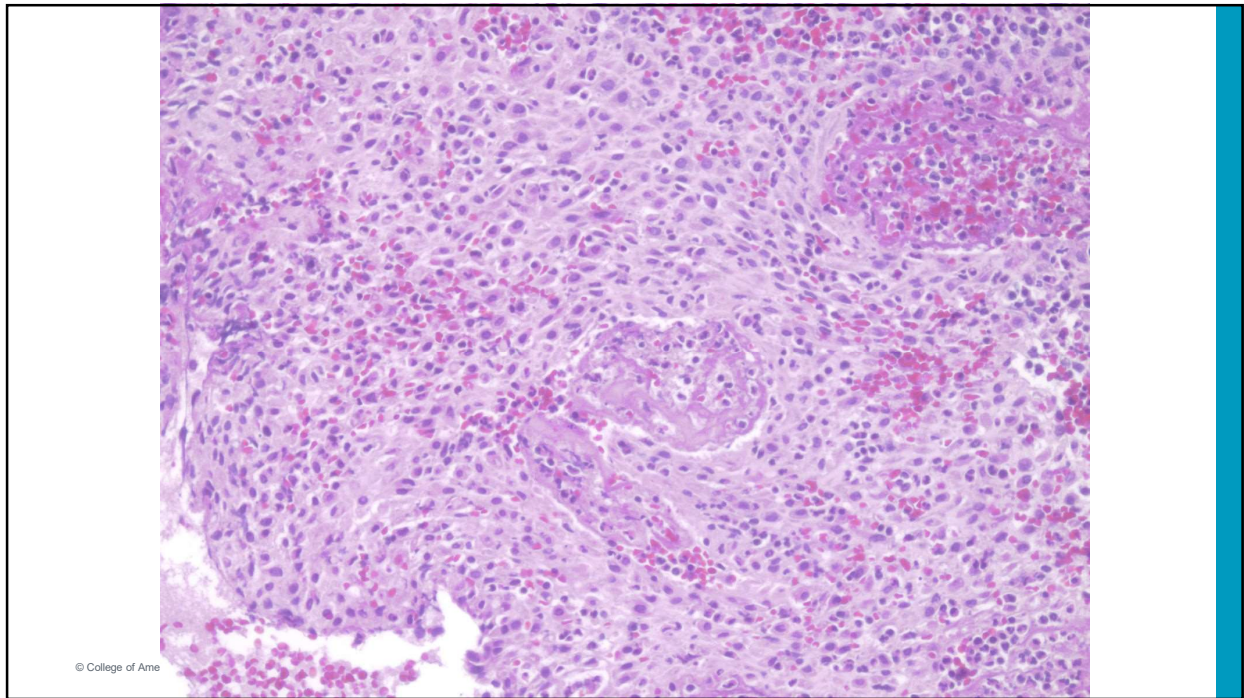
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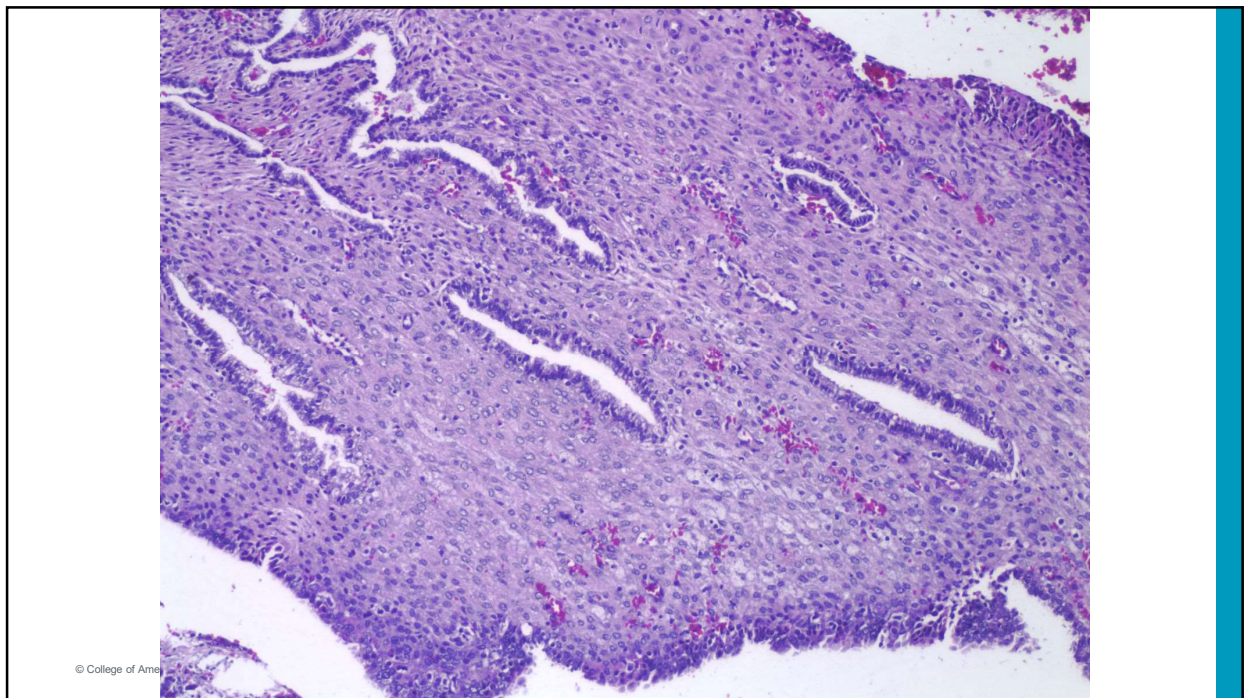
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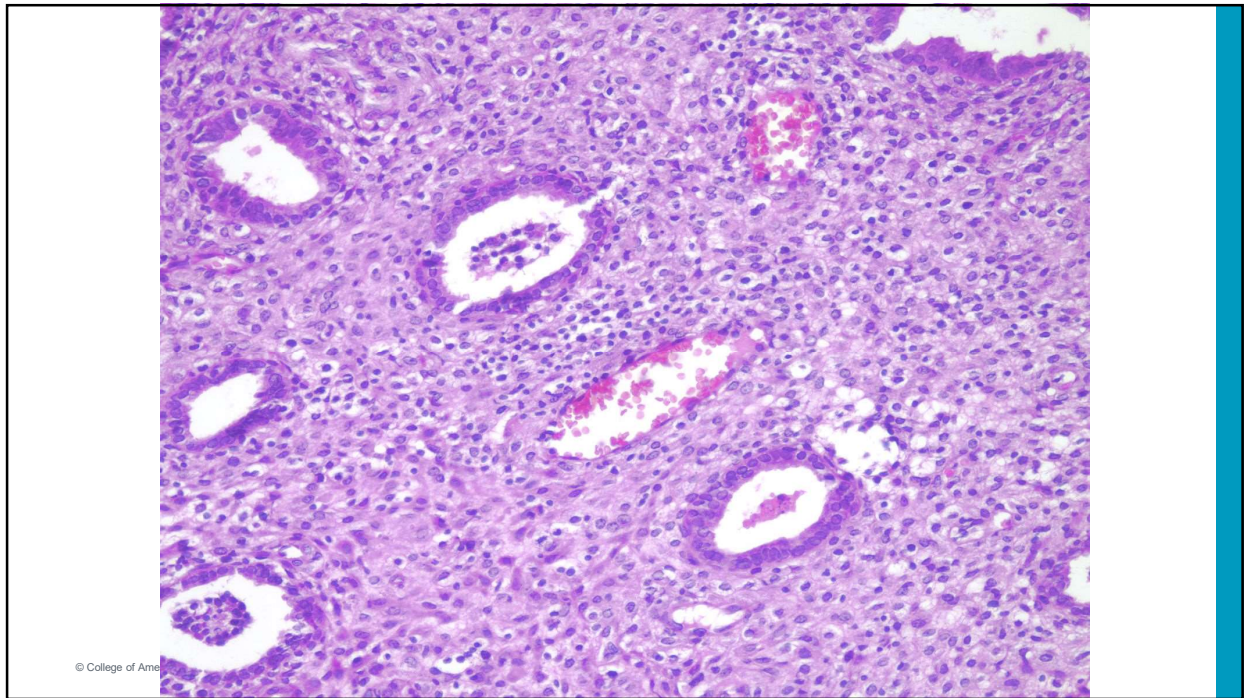
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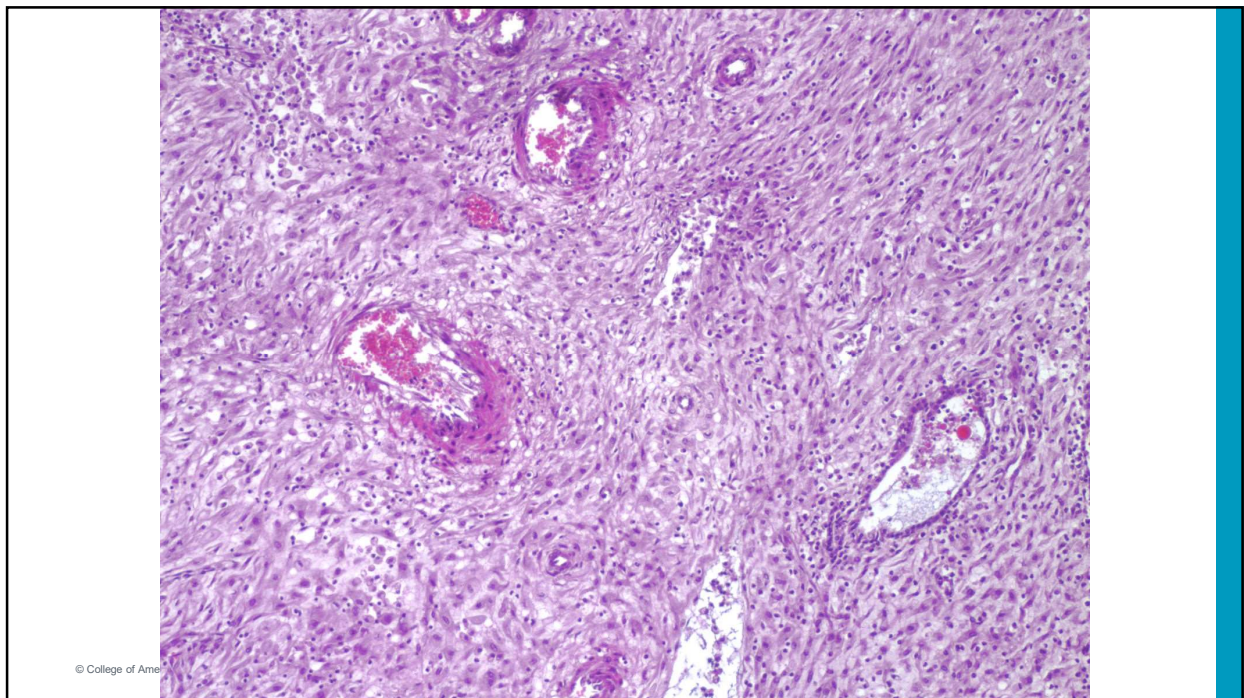
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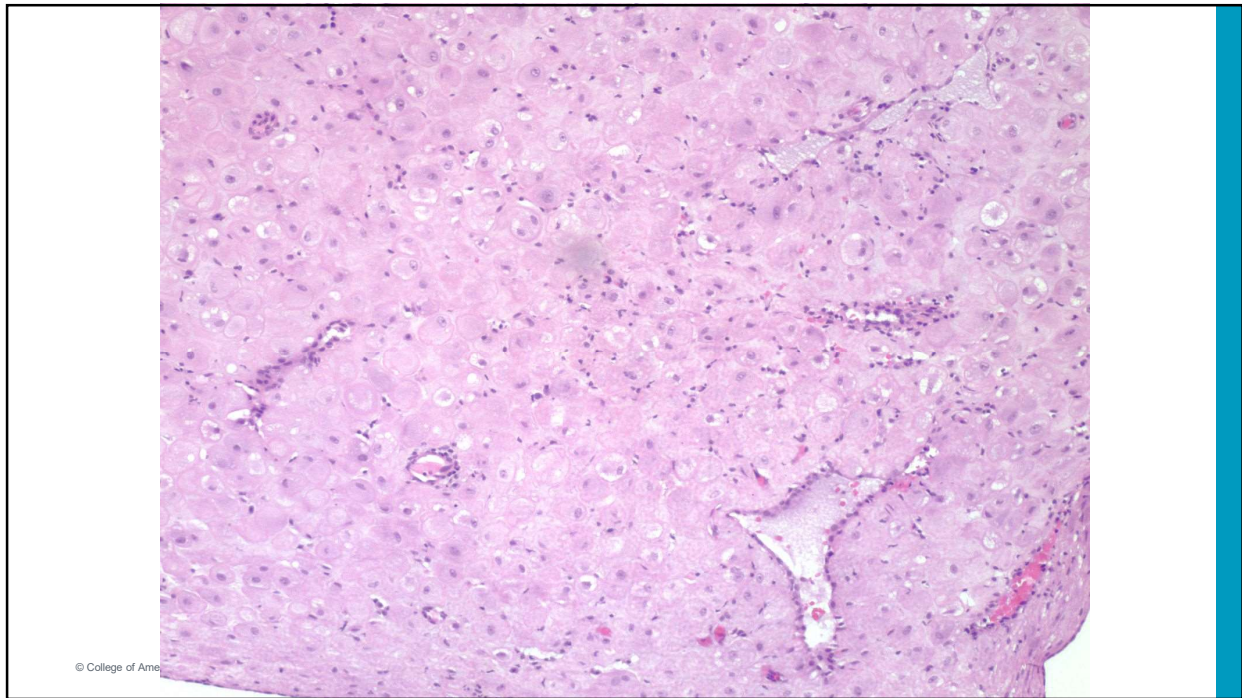
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Progesterone-coated IUD

- **Mirena coil (levonorgestrel)**
 - **Pseudodecidualization (also seen in endocervix)**
 - **Mucinous metaplasia**
 - **Infiltration by pmns and plasma cells**
 - **Stromal hyaline nodules**
 - **Surface syncytial/papillary change**
 - **Infarcted decidua**
 - **Dystrophic calcification**
 - **Hemosiderophages**

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Exogenous hormone effect: hormone replacement therapy

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Long-term HRT

- **More vaginal bleeding, increased endometrial thickness**
- **No increase in endometrial carcinoma or hyperplasia**
- **More often benign endometrial cells on Pap**
- **Less often abnormal endometrial histology**

Mossa et al, Eur J Gynaecol Oncol. 2003;24:507

Mount et al, Obstet Gynecol. 2002;100:445

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Hormone Replacement Therapy

- **Combination: conjugated equine estrogen (i.e. Premarin) + medroxyprogesterone acetate (Provera)**
 - cyclic regimen: Provera added in the second half of the cycle (bleeding)
 - continuous HRT - daily Provera (breakthrough bleeding in 20%)

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Hormone Replacement Therapy

- **Cyclic regimen:**
 - Weakly proliferative, some with residual stromal predecidual change
 - Subnuclear vacuoles
 - Bleeding pattern (non-menstrual)
 - Atrophy in some cases
- **Continuous regimen:**
 - Inactive, atrophy or insufficient
 - Metaplasias more common

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Hormone Replacement Therapy

- **Cyclic regimen:**

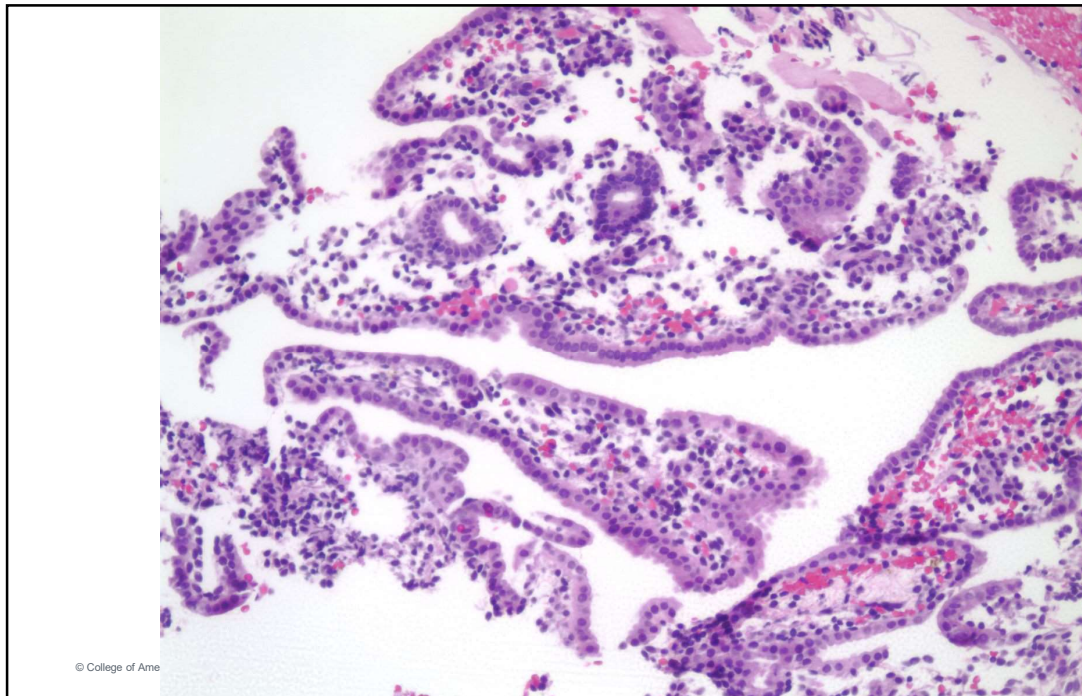
- More risk of endometrial cancer
- If proliferative pattern during progestin phase, suggest insufficient progestin dose
- If decidualized during estrogen phase, progestin dose too high
- Atrophy – endometrium is not responding

- **Continuous regimen:**

- Almost no risk of endometrial cancer

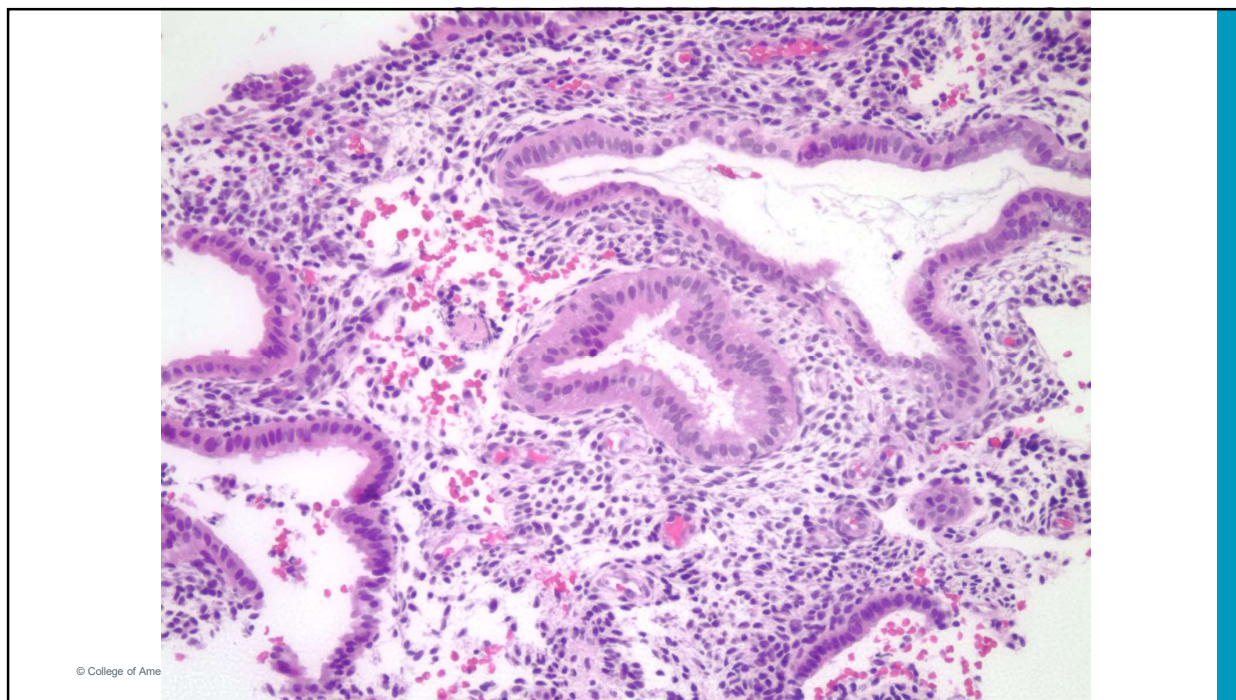
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Antineoplastic therapy effect

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Tamoxifen

- **Synthetic non-steroidal estrogen derivative**
- **Binds to estrogen receptors**
- **High levels of estrogen (before menopause) - antiestrogenic effect**
- **Low levels of estrogen (menopause) - weak estrogenic effect**

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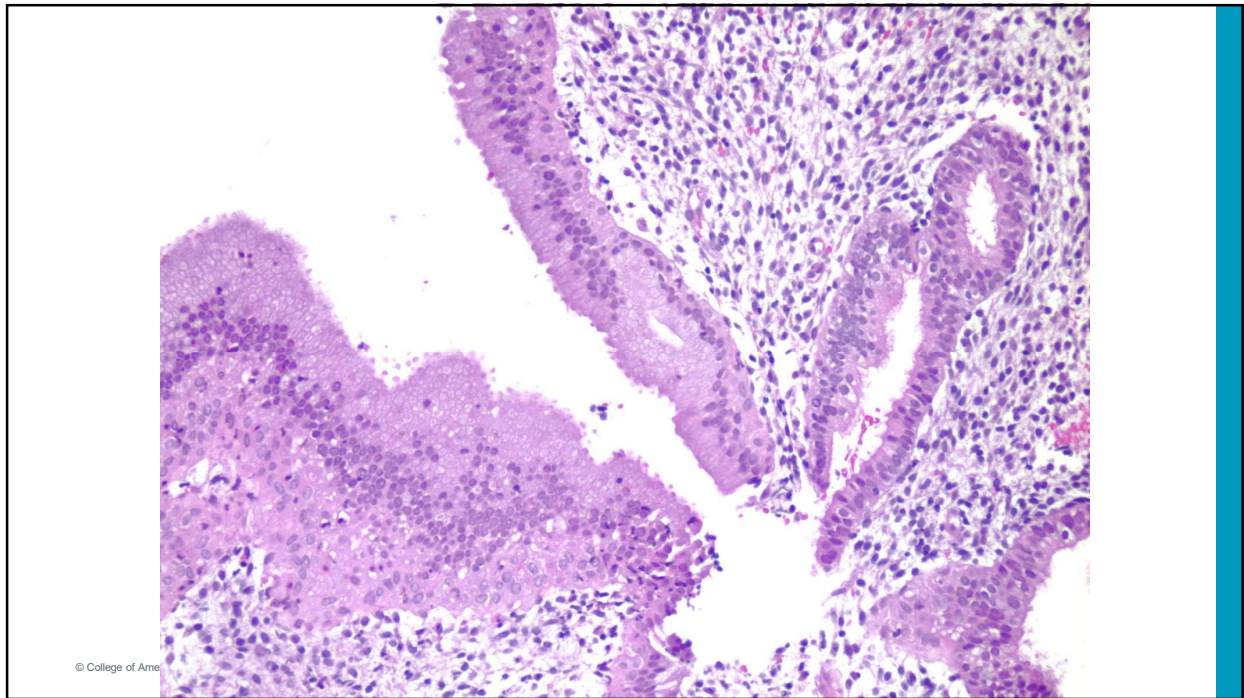
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Tamoxifen

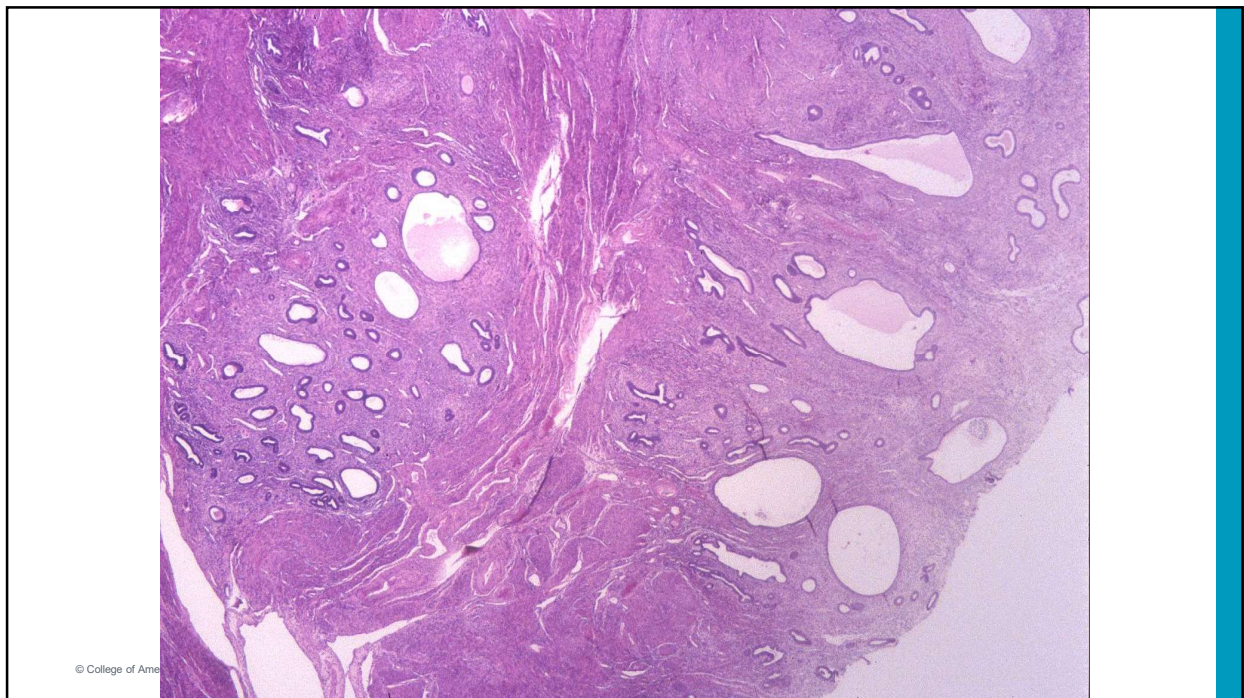
- **Atrophy**
- **Polyps**
- **Metaplasias**
 - **Mucinous, papillary, ciliated, eosinophilic**
- **Diffuse fibrosis of stroma**
- **Smooth muscle metaplasia of the stroma, growth of leiomyomas**
- **Adenomyosis, endometriosis**

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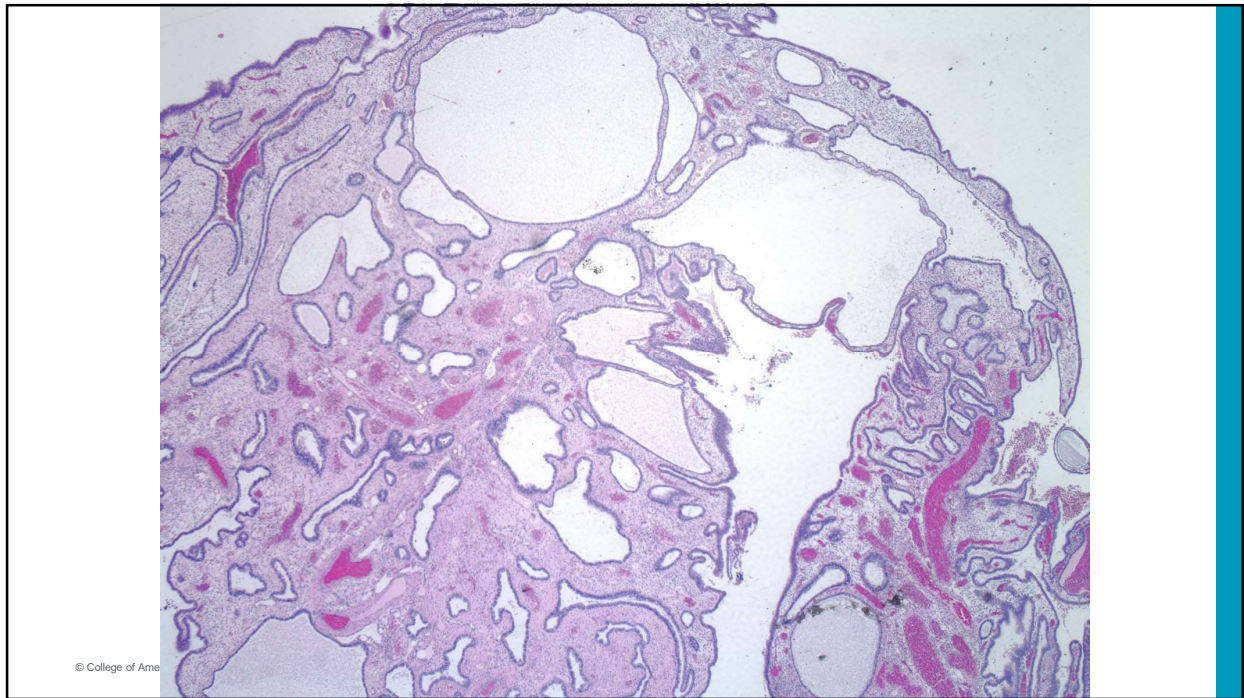
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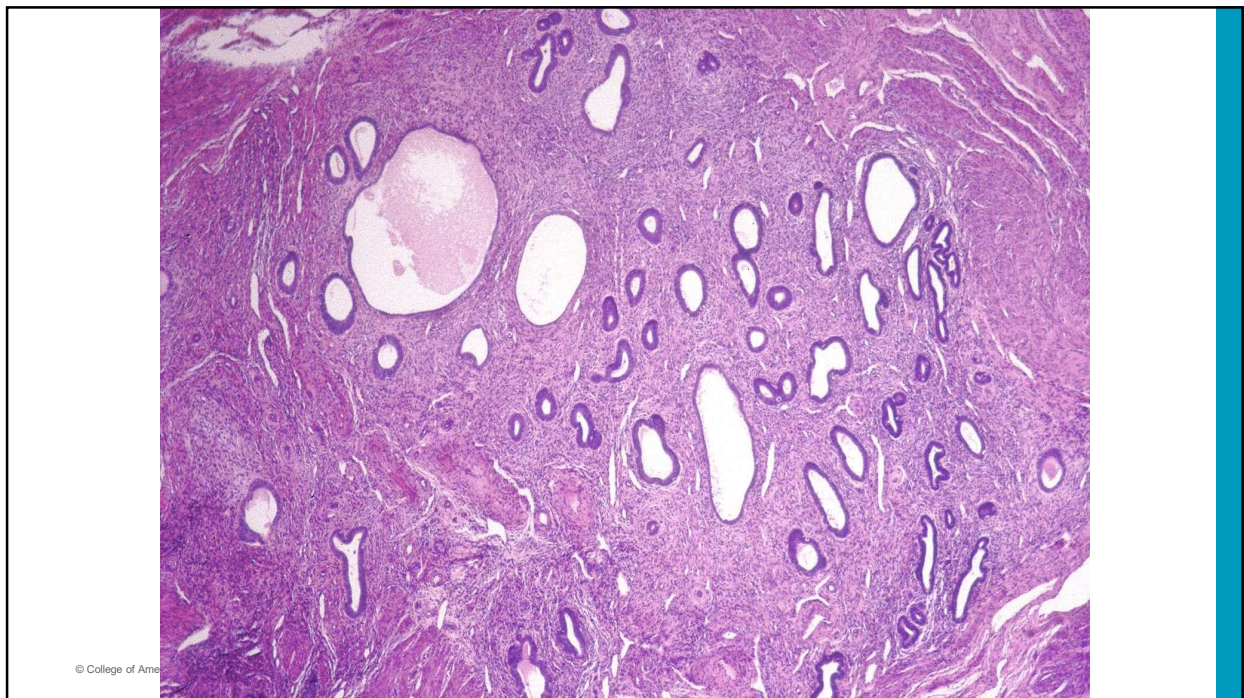
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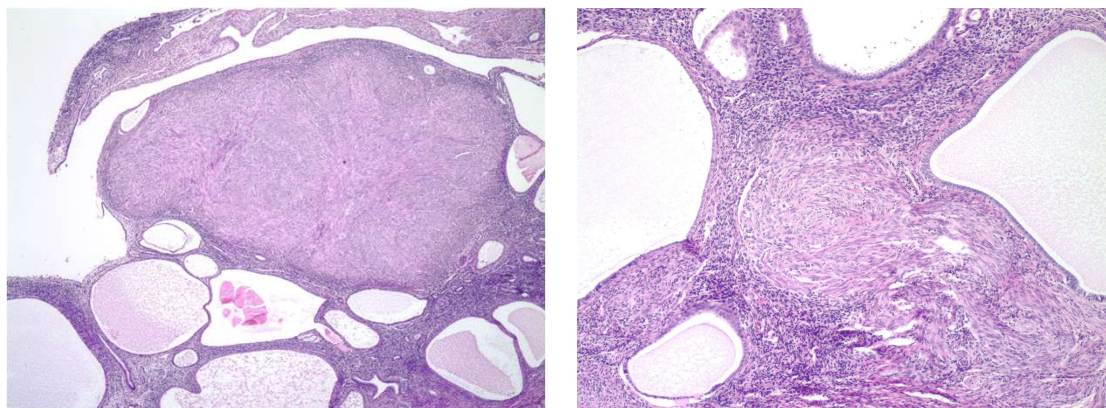
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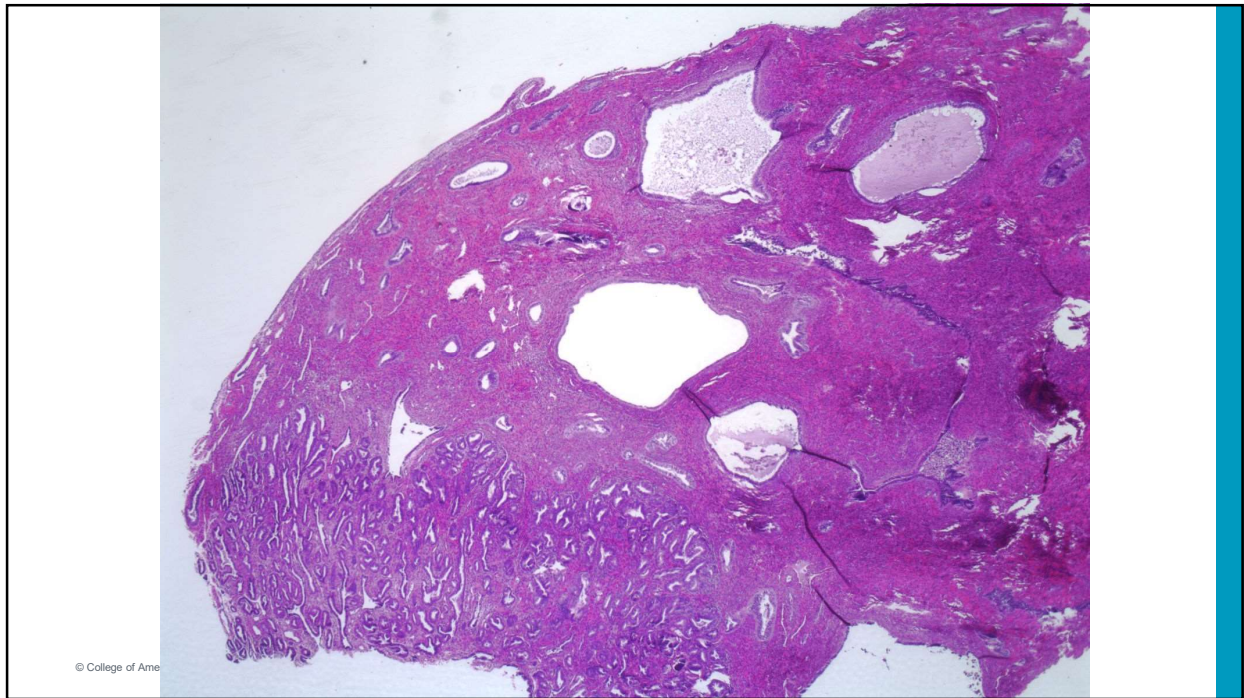
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Tamoxifen Rx

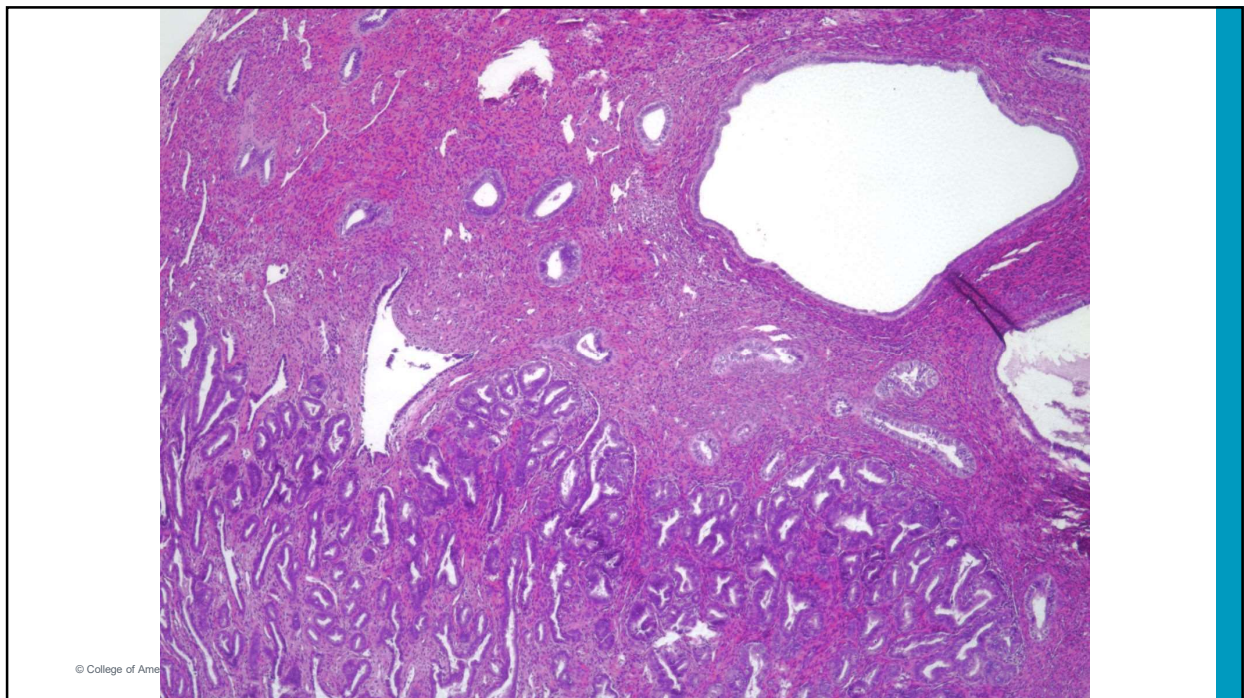
- **Hyperplasia**
- **Carcinoma – low grade endometrioid**
- **Long duration/high cumulative dose**
 - Serous/clear cell carcinoma
 - Carcinosarcoma
 - Adenosarcomas (rare), some in endometriosis
 - Rare leiomyosarcomas

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SERMs

Newer selective estrogen modulators (Tamoxifene was first)

Raloxifene

- Tamoxifen increases endometrial proliferation and upregulates estrogen receptors
- Raloxifene does not

Bazedoxifene – neutral effect on endometrium

Lasofloxifene increases endometrial thickness, polyps

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Aromatase Inhibitors

- Aromatase inhibitors- **Arimidex, Letrozole**
- In addition to breast cancer, used for Rx of endometriosis
 - ATAC trial (Arimidex, Tamoxifen, alone or in combination) (*J Obstet Gynaecol.* 2010;30(6):596-604)
 - No significant difference in endometrial pathology between AIs and Tamoxifen

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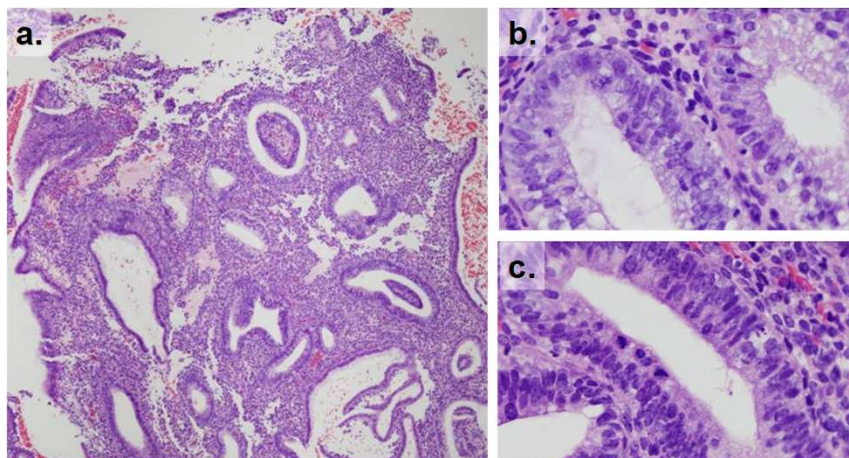
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Selective Progesterone Modulators

- Mifepristone (RU486)
- Rx of leiomyomas, endometriosis
- Premenopausal women
- Thickened endometrial stripe
- Progesterone receptor modulator-associated endometrial changes ('PAEC')
 - Unique constellation
 - Massive cystic dilatation, non-physiologic secretory changes, apoptosis, abnormal celsels
 - Often misdiagnosed as hyperplasia

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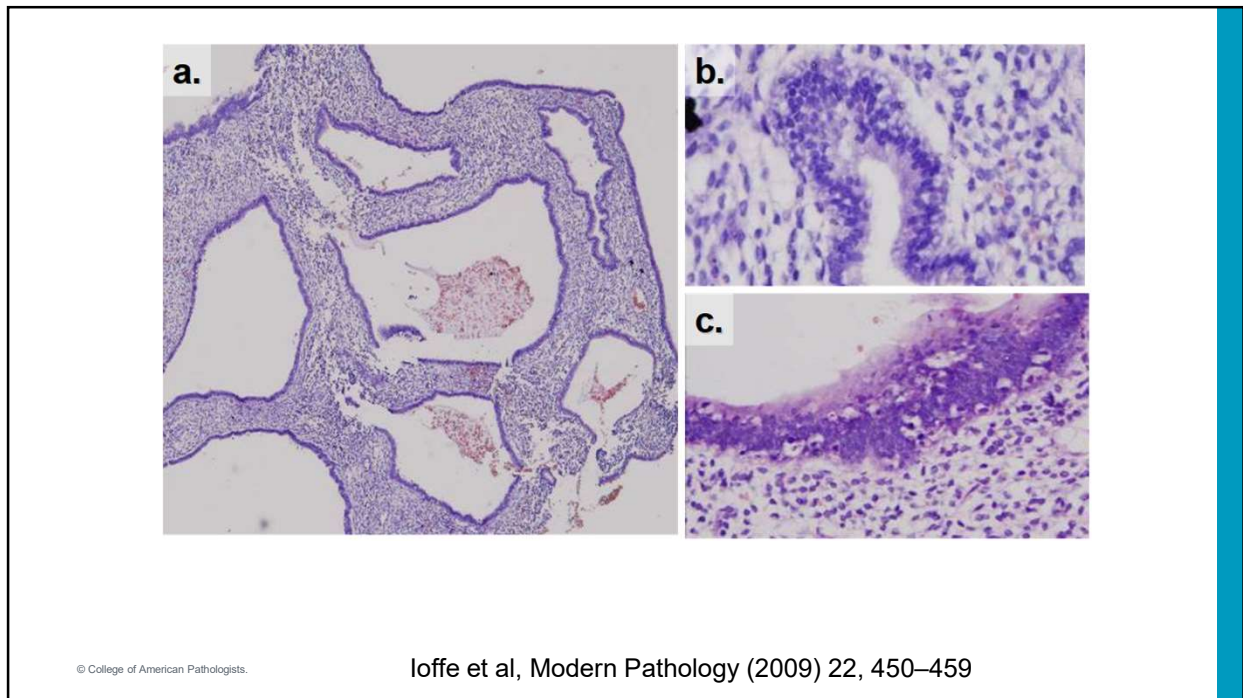
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Ioffe et al, Modern Pathology (2009) 22, 450–459

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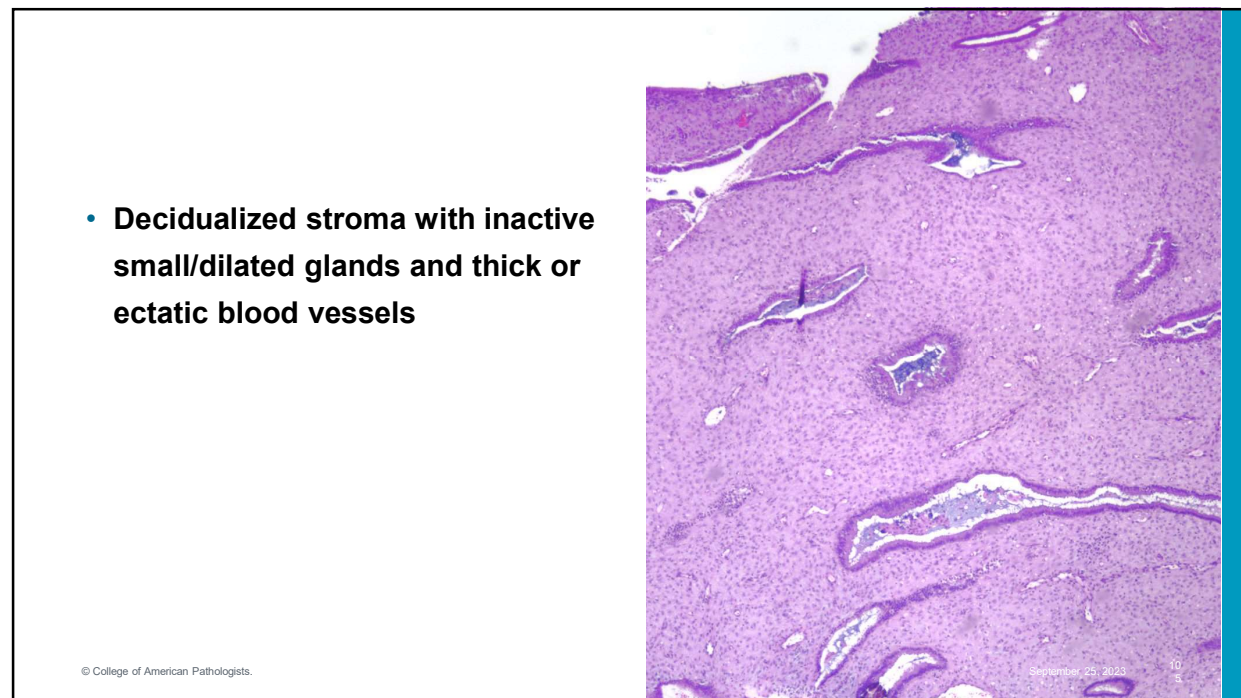
103

Progestin Therapy

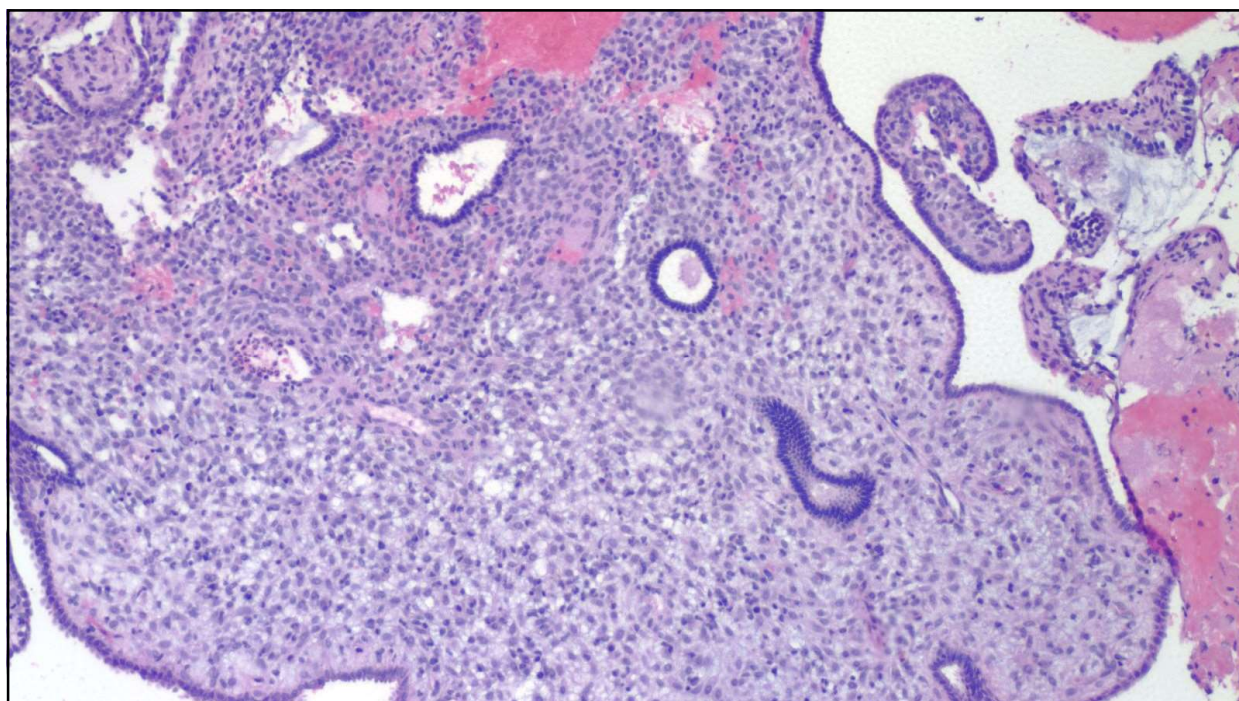
- **High-dose progestins**
 - Rx of endometrial hyperplasia in premenopausal women; bx after 6-12 weeks, 6 and 12 months
 - Decidualized stroma with inactive small/dilated glands and thick or ectatic blood vessels
 - Residual areas of endometrial hyperplasia without visible progestin effect

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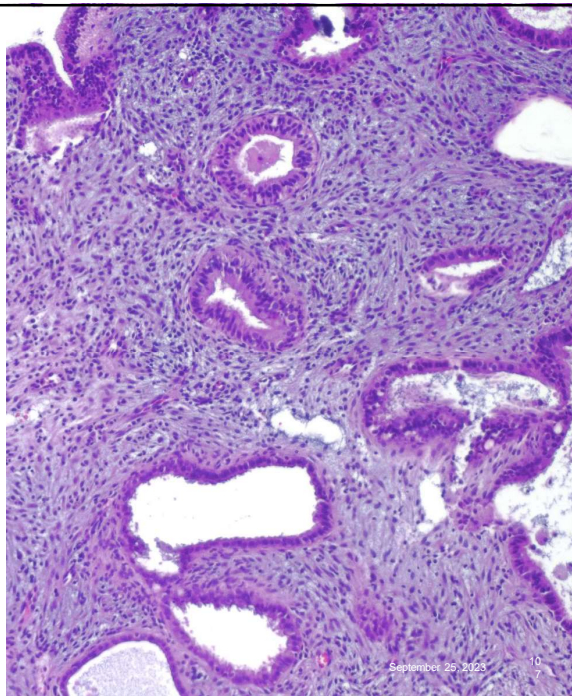


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No cytologic atypia determination can be made

- Mucinous, secretory, squamous, and eosinophilic metaplasia

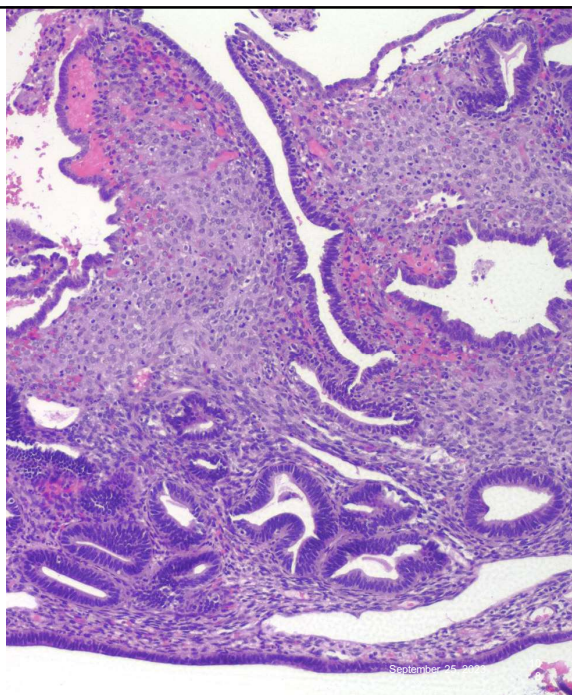
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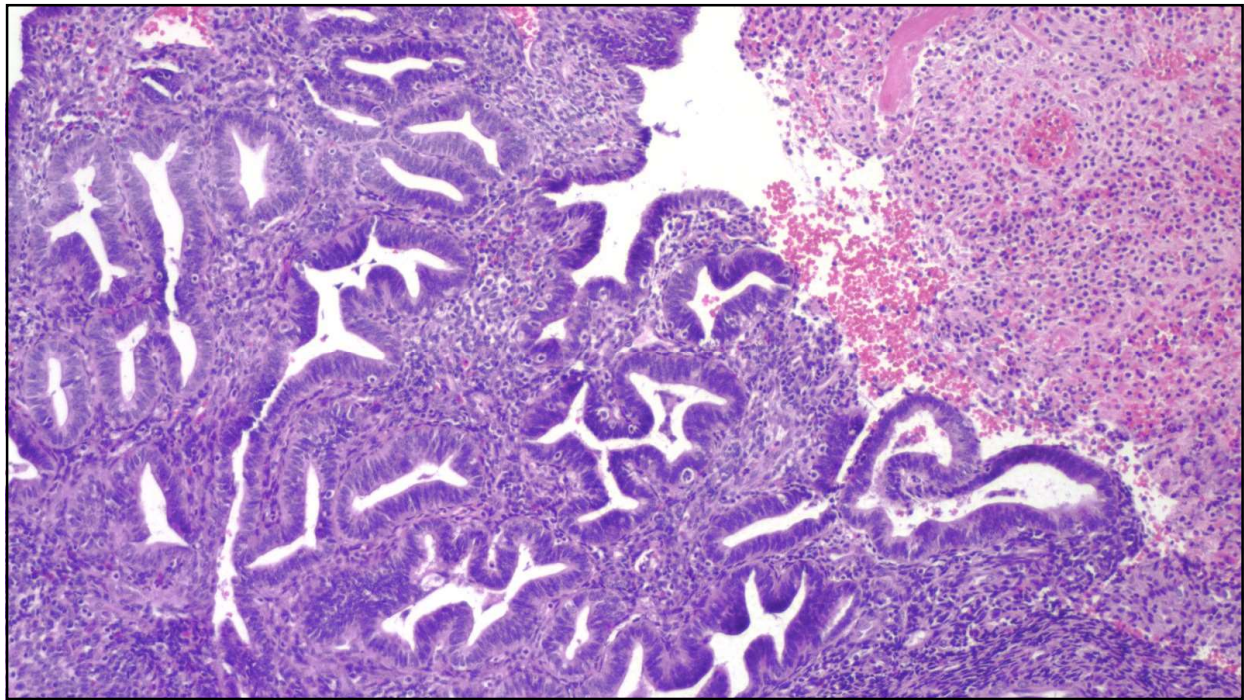
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- Residual hyperplasia/carcinoma shows no exogenous hormone effect

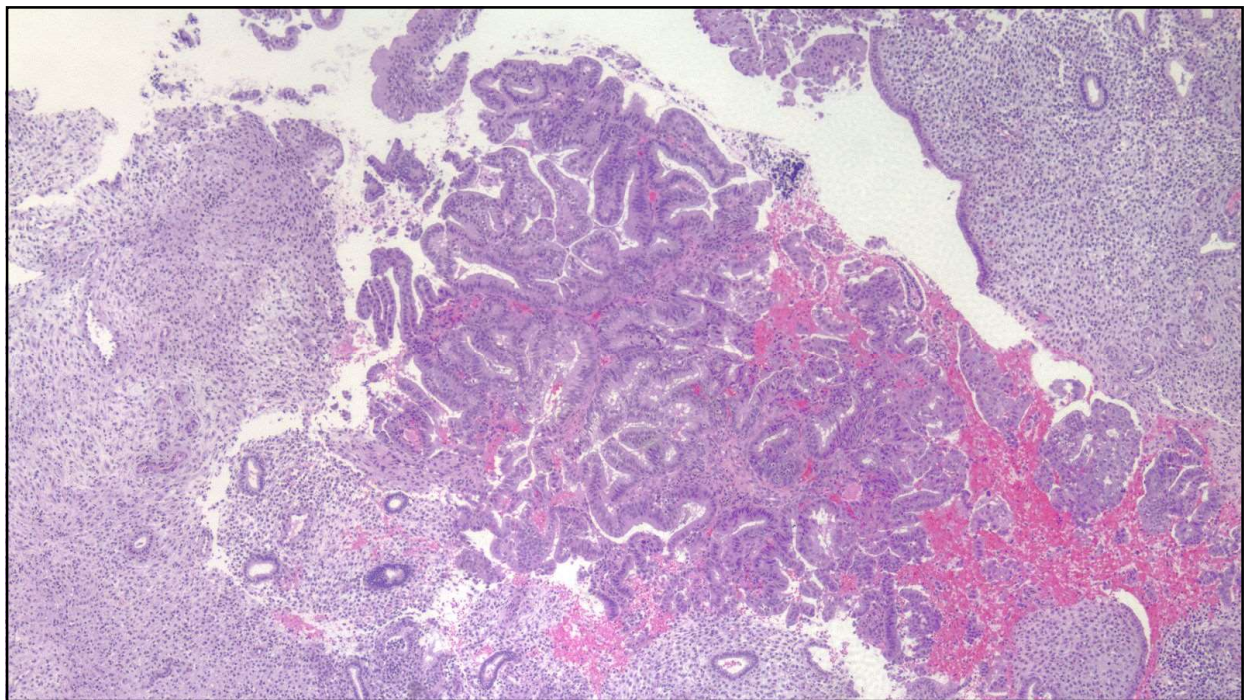
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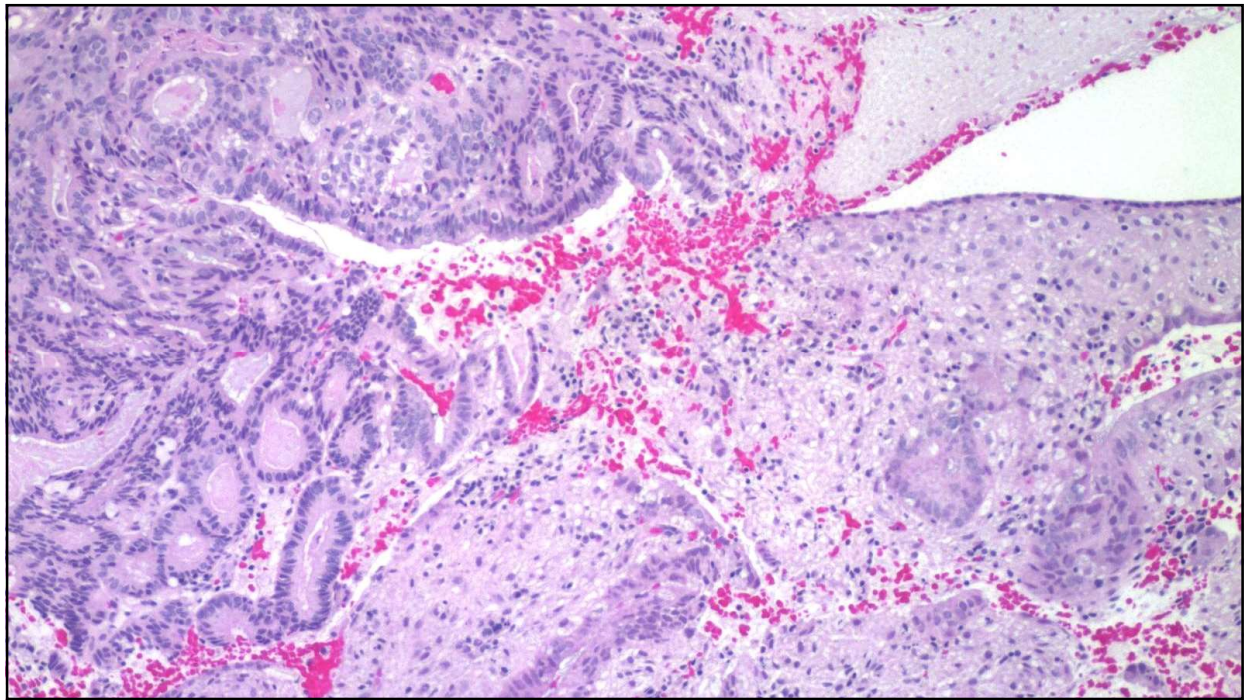
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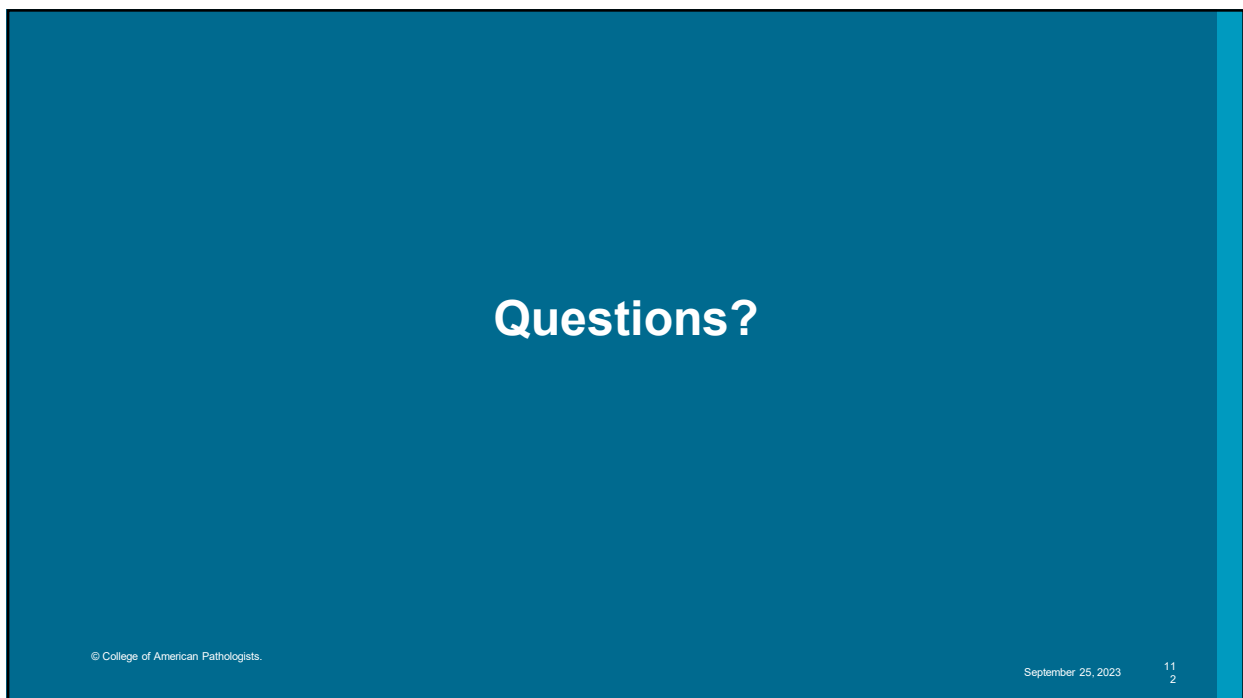
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