DIAGNOSIS, CLASSIFICATION AND TERMINOLOGY OF PREMALIGNANT LESIONS OF THE ENDOMETRIUM

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TO DISCUSS

- endometrial hyperplasias
- possible precursors of type 2 endometrial cancers

ENDOMETRIAL HYPERPLASIAS

- current classification (WHO 2014)
- clinical significance of different types of hyperplasia
- morphological features
- mimics of hyperplasia
- distinction between atypical hyperplasia and grade 1 endometrioid adenocarcinoma
- hyperplasia in polyps
- effects of hormonal treatment
- alternative classifications- EIN (endometrial intraepithelial neoplasia) and European Working Group Classification

WHO (1994/2003)

1. **Simple hyperplasia**
   a) **without atypia**
   b) **with atypia**

2. **Complex hyperplasia**
   a) **without atypia**
   b) **with atypia**

SIMPLIFIED CLASSIFICATION (WHO 1994/2003)

- simple hyperplasia
- complex hyperplasia
- atypical hyperplasia

WHO Classification of Tumours of Female Reproductive Organs
Consensus and Editorial meeting, IARC, Lyon, 13–15 June 2013

WHO 2014

- endometrial hyperplasias “collapsed” into 2 categories
- simple and complex hyperplasia- **hyperplasia without atypia**/non-atypical hyperplasia
- atypical hyperplasia (endometri**OID** intraepithelial neoplasia/ EIN is acceptable synonym)

HYPERPLASIA WITHOUT ATYPIA

- WHO definition- an exaggerated proliferation of glands of irregular size and shape, with an associated increase in the gland to stroma ratio compared with proliferative endometrium but without significant cytological atypia
- most (especially simple hyperplasia) are response to prolonged oestrogen exposure unopposed by progesterone (analogous to disordered proliferative endometrium)
- at present use both old and current WHO eg hyperplasia without atypia (simple hyperplasia)

ATYPICAL HYPERPLASIA- WHO 2014

- distinction between endometrial hyperplasia without atypia and AH/ EIN is based on nuclear atypia which may include enlargement, pleomorphism, rounding, loss of polarity and nucleoli

PRESUMED SIGNIFICANCE

- hyperplasia without atypia has low risk of progression to endometrioid carcinoma
- atypical hyperplasias may coexist with and have significant risk of progression to endometrioid carcinoma
- hyperplasia without atypia is usually treated with hormonal agents
- atypical hyperplasia is usually treated by surgery
- some atypical hyperplasias (and low grade endometrioid carcinomas) can be treated hormonally (fertility sparing, PCOS, poor anaesthetic risk, increased BMI)
- many hyperplasias without atypia are managed surgically

RISK OF PROGRESSION

- no one really knows
- impossible and unethical to design study
- treatment instigated once hyperplasia diagnosed
- most assumptions based on single “seminal” paper (Kurman RJ et al. The behaviour of endometrial hyperplasia. A long-term study of “untreated” endometrial hyperplasia in 170 patients. Cancer 1985; 56;403-412) (patients did not undergo hysterectomy for at least 1 year)
- 1 of 93 (1%) with SH, 1 of 29 (3%) with CH, 11 of 48 (23%) with AH progressed to carcinoma (other studies 40-50% of AH “progress” to carcinoma) (but ? progression, ? undersampling, ? adenocarcinoma all along)
- THIS PAPER SUGGESTED CYTOLOGICAL ATYPIA IS THE MOST IMPORTANT FACTOR AND THIS HAS BEEN PROPAGATED IN THE LITERATURE

INTEROBSERVER VARIATION IN CLASSIFICATION OF ENDOMETRIAL HYPERPLASIAS

- **Bergeron et al. AJSP 1999; 23; 1102-1108**
- **Kendall et al. AJSP 1998; 22; 1012-1019**
- **Skov et al. IJGP 1997; 16; 33-37**
- **Zaino et al. Cancer 2006; 106;804-811**
- **Allison et al. AJSP 2008;32;691-698**

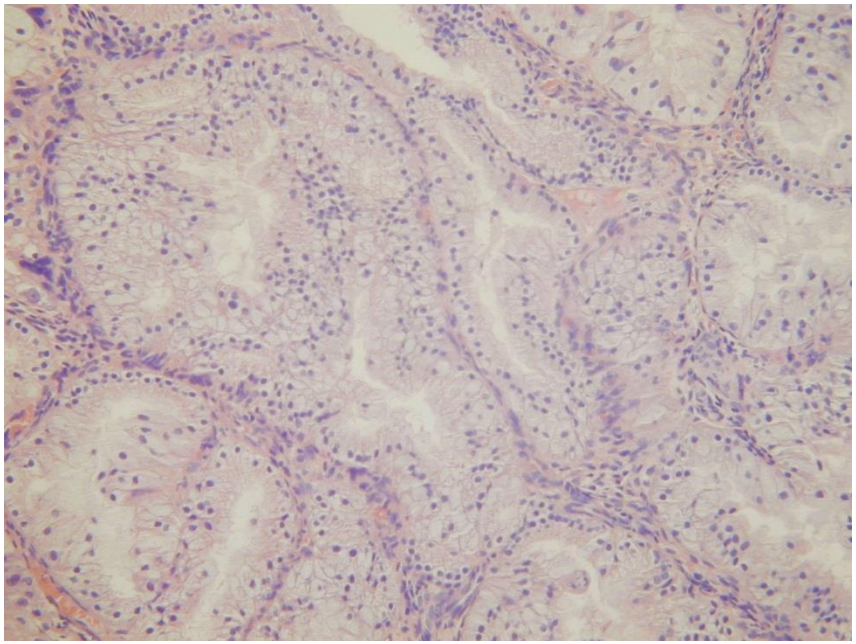
INTEROBSERVER VARIATION

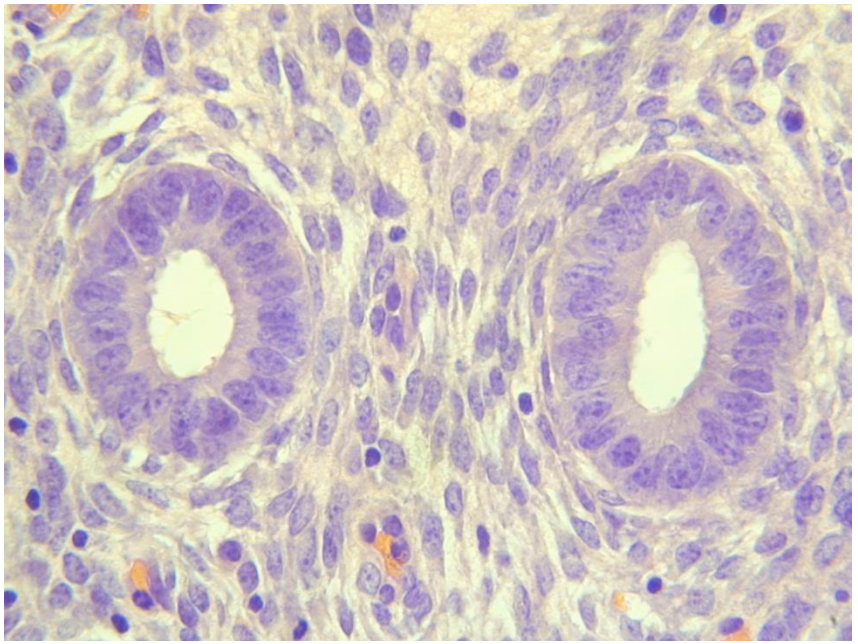
- significant interobserver variation
- main problem is assessment of nuclear atypia
- assessment of nuclear atypia is extremely subjective

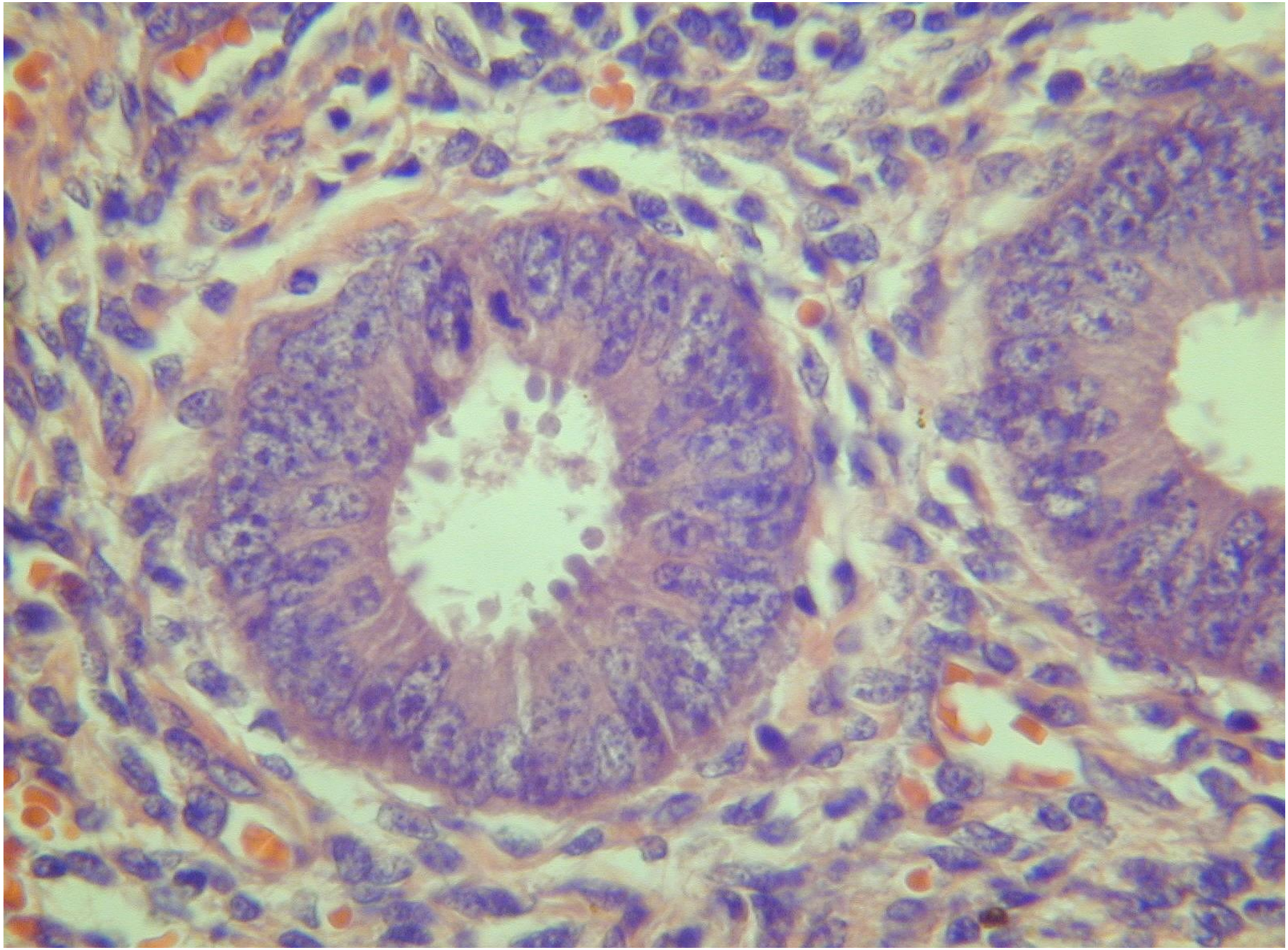
RECENT REALISATION

- undue emphasis on nuclear atypia
- architecture very important
- recent EIN studies confirm this

NUCLEAR ATYPIA

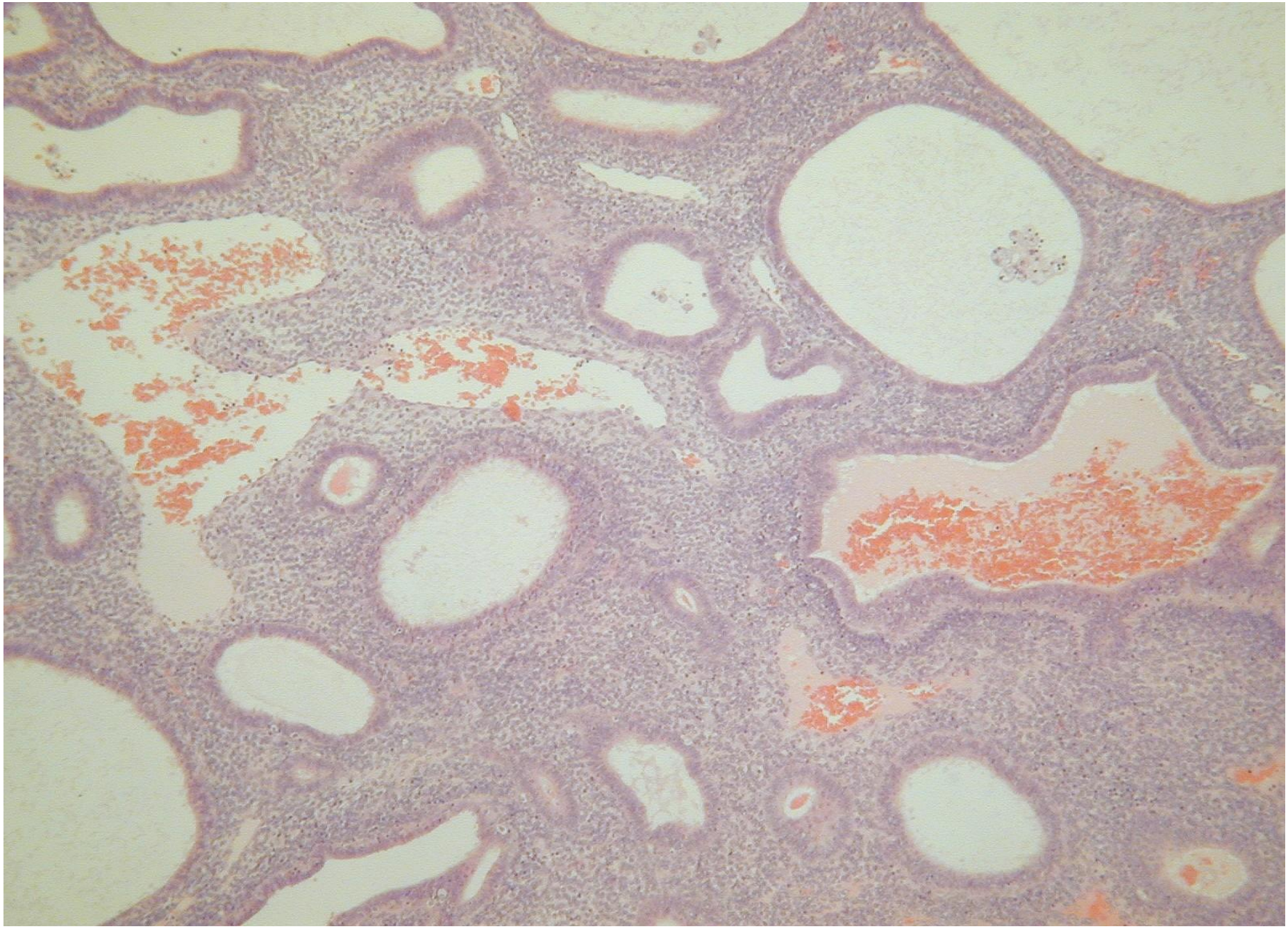




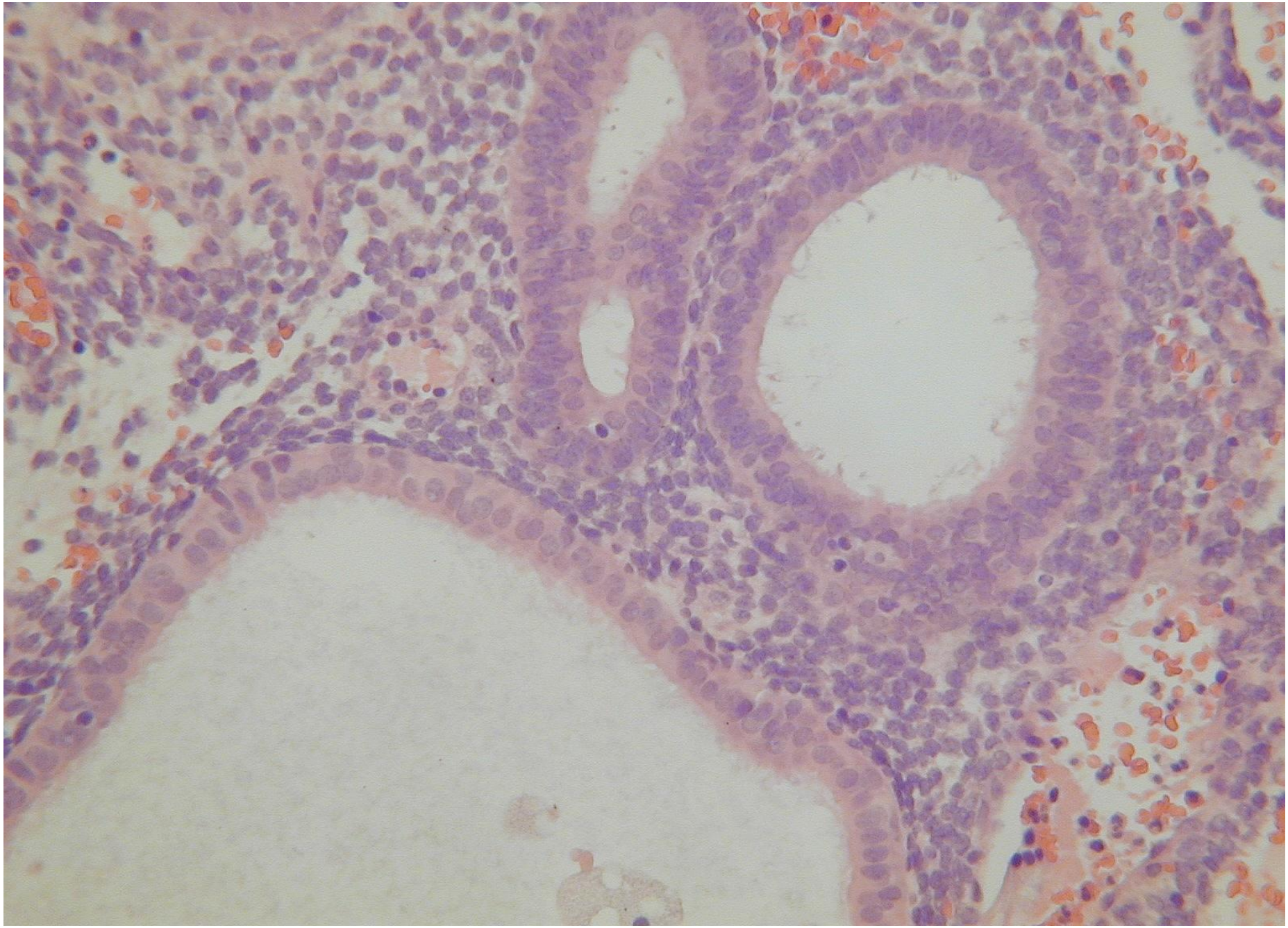


MORPHOLOGICAL FEATURES OF ENDOMETRIAL HYPERPLASIA

- SH- mild or no increase in gland to stroma ratio; dilated glands; proliferative activity; often ciliated metaplasia and surface breakdown
- CH- significant increase in gland to stroma ratio; proliferative activity; maintenance of nuclear polarity; no glandular confluence/stromal exclusion
- AH- increase in gland to stroma ratio; proliferative activity; nuclear changes (rounding, loss of polarity, nucleoli); no glandular confluence/stromal exclusion/cribriform architecture



HYPERPLASIA WITHOUT ATYPIA- SH



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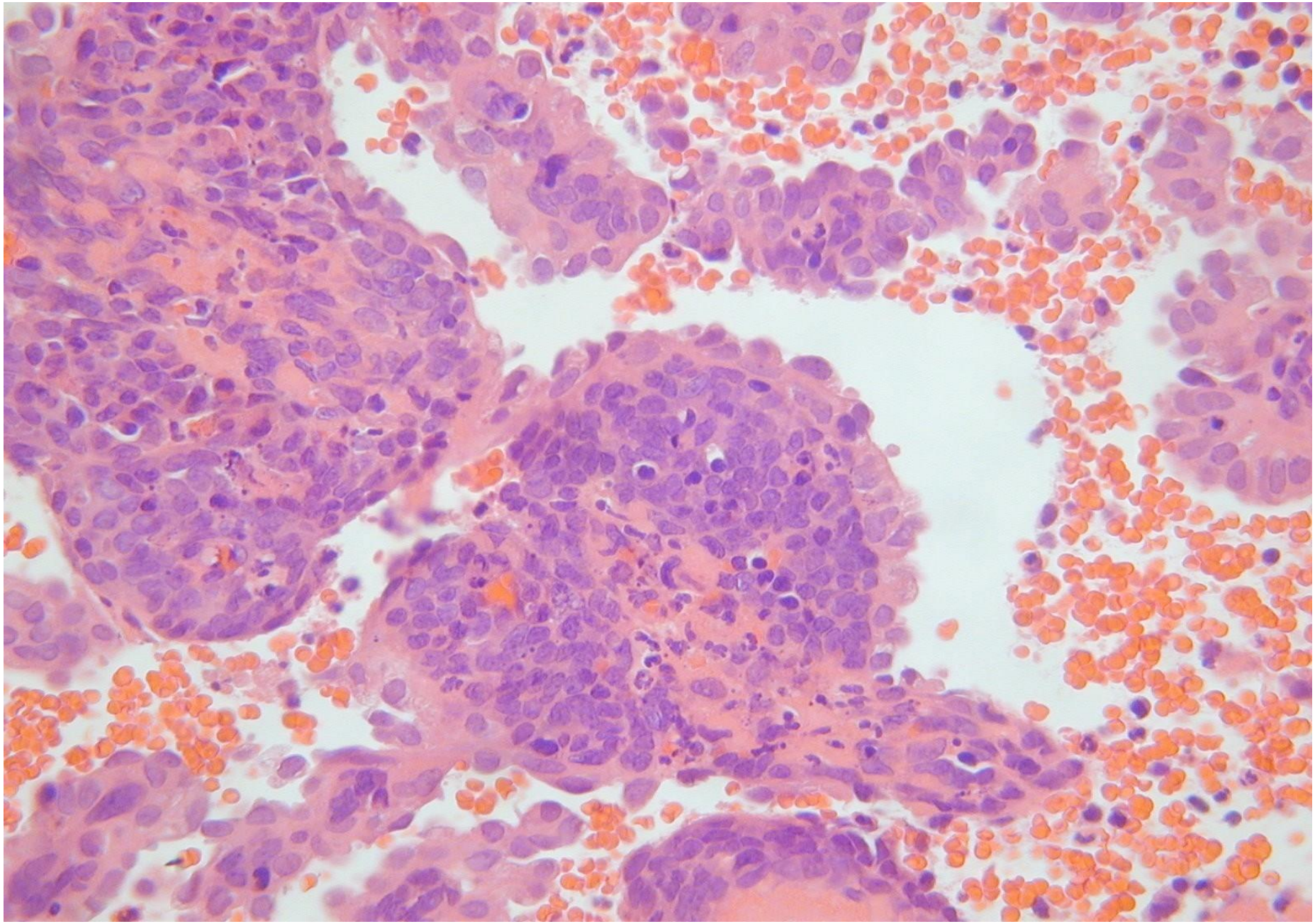

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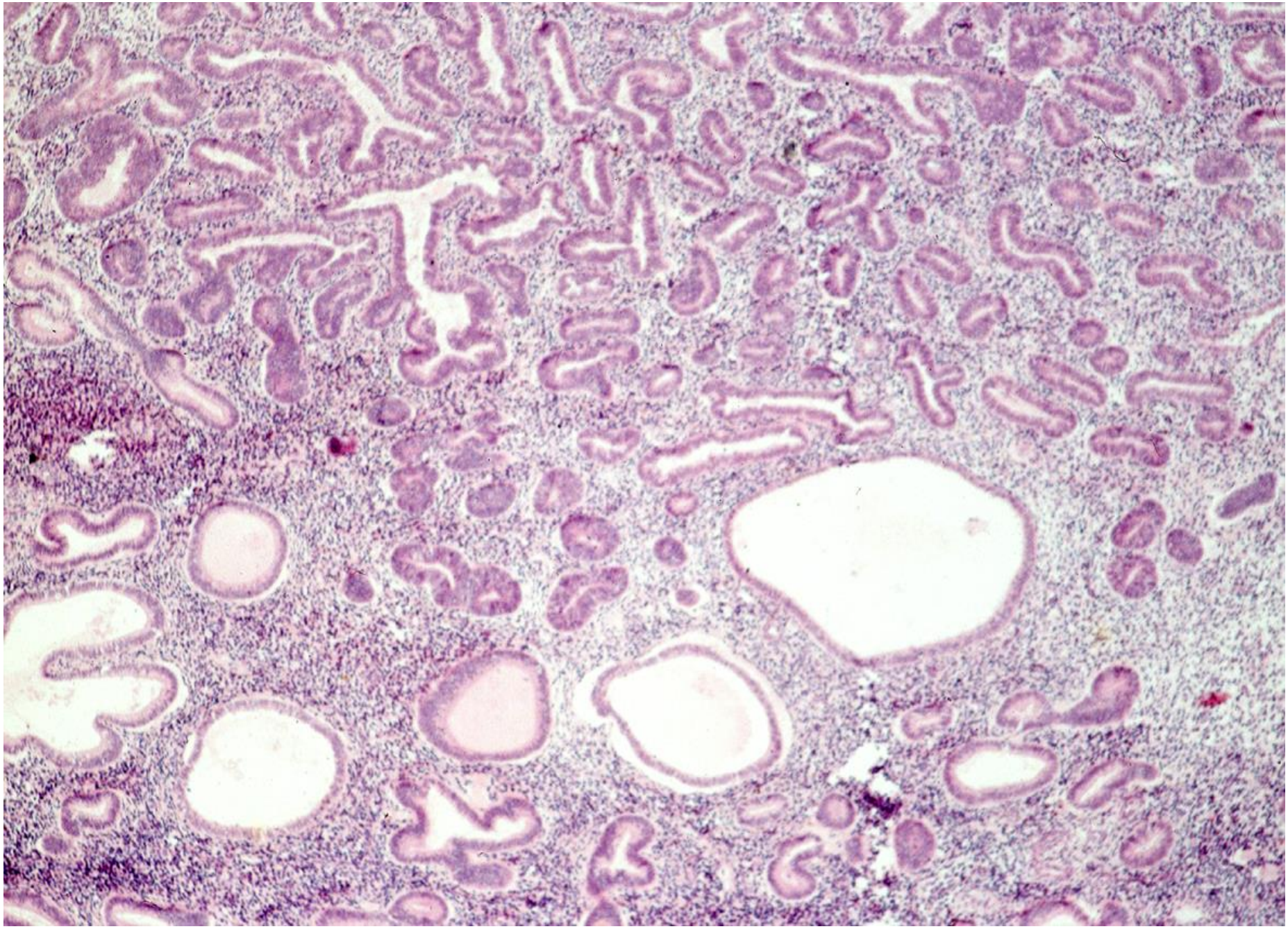
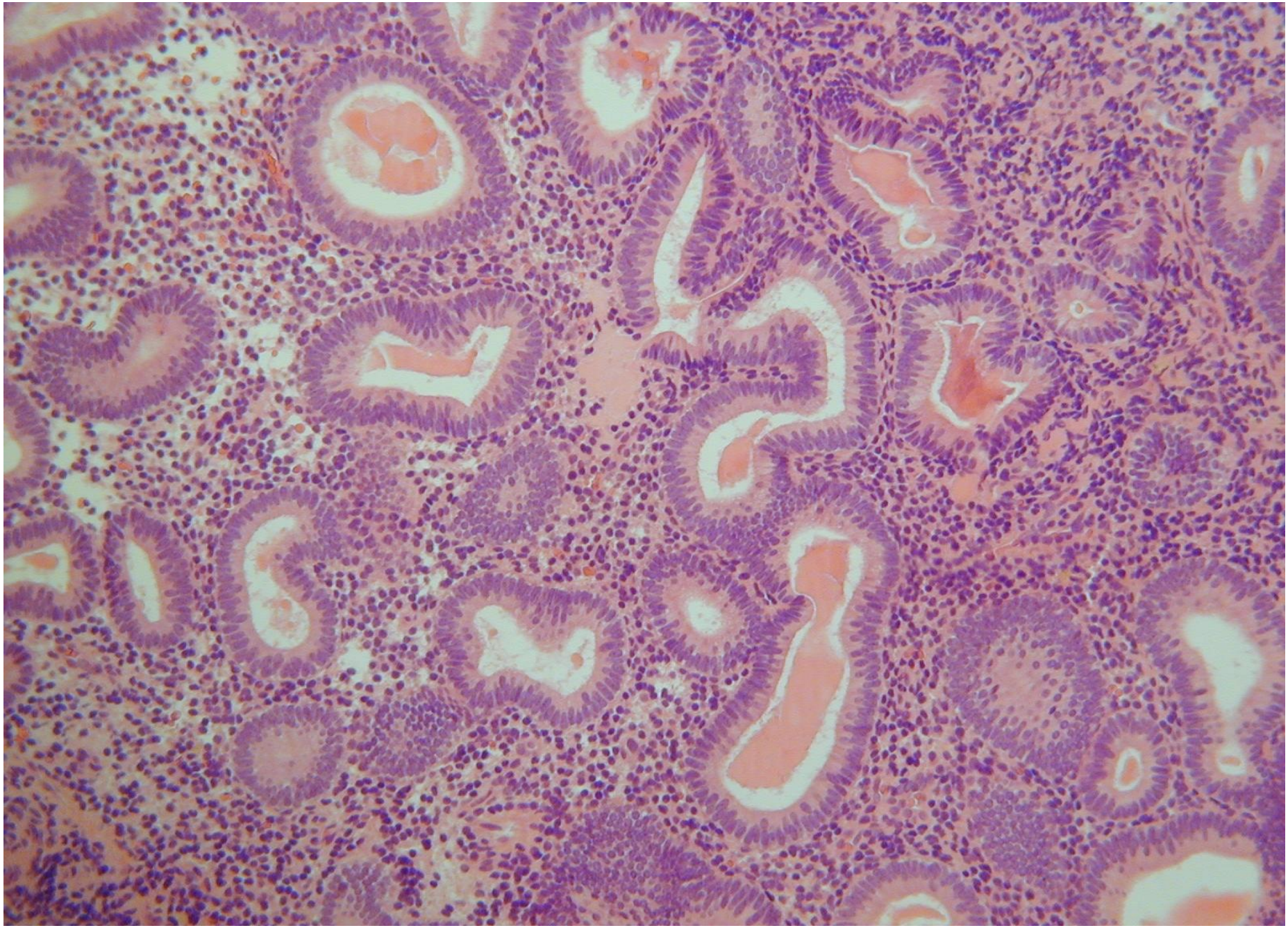


HYPERPLASIA WITHOUT ATYPIA- CH



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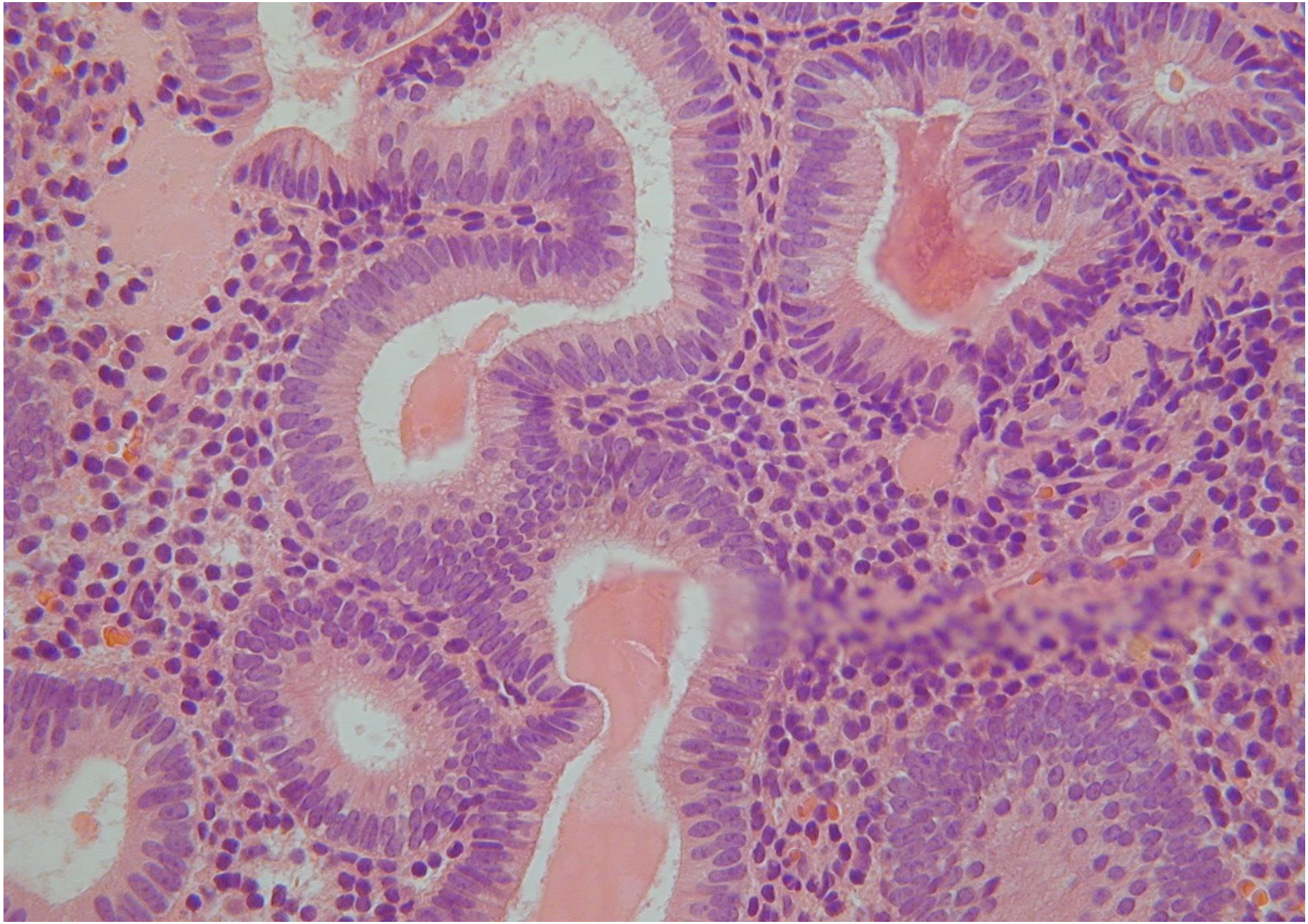

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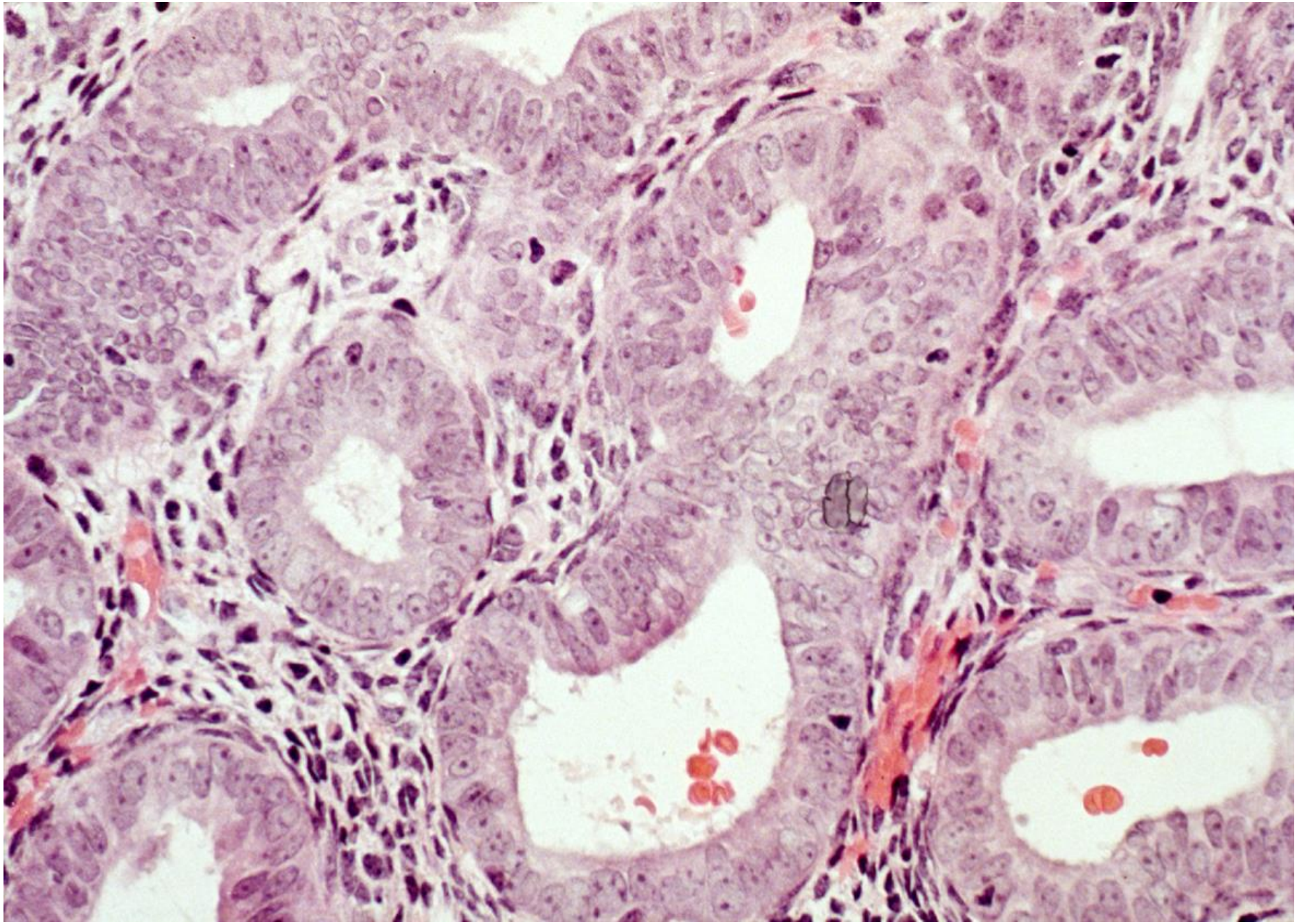
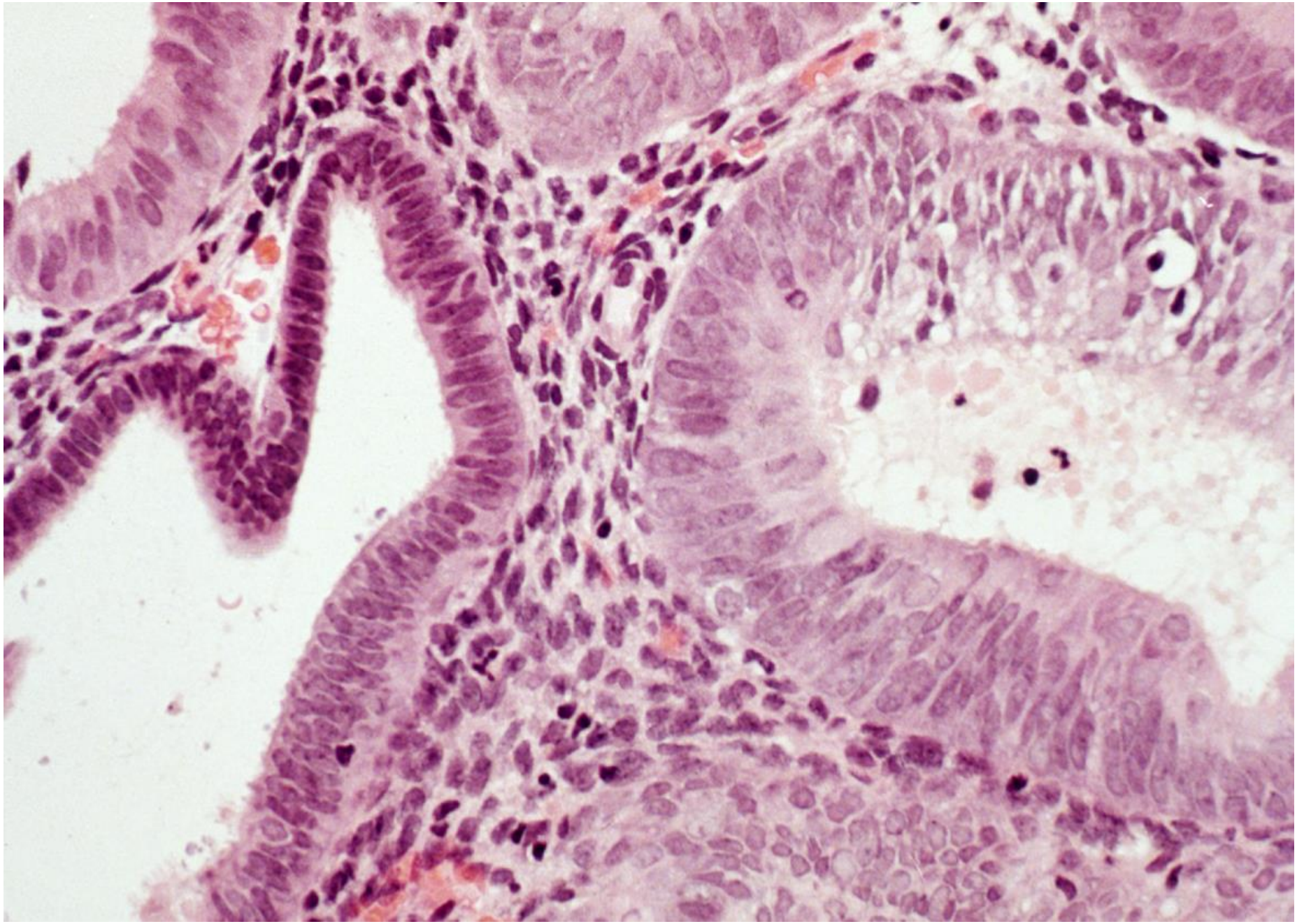


AH



AH

ATYPICAL HYPERPLASIA

- spectrum (useful to say if at upper or lower end of spectrum)
- some are endometrioid adenocarcinoma (reluctance of pathologist to diagnose- young or limited tissue, criteria for invasion)
- high risk of subsequent cancer (undersampling, cancer all along, progression)

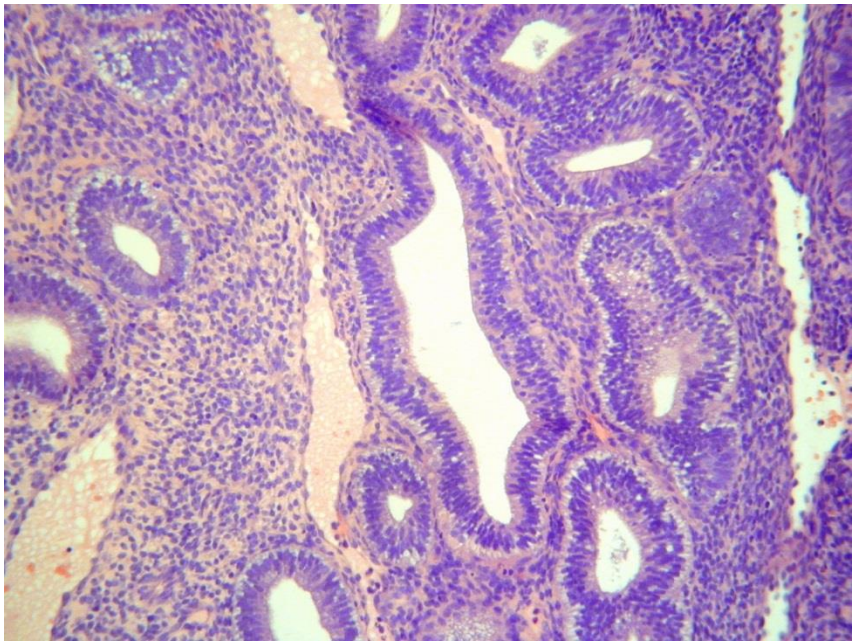
CRITERIA FOR ATYPICAL HYPERPLASIA (ALL MUST BE FULFILLED)

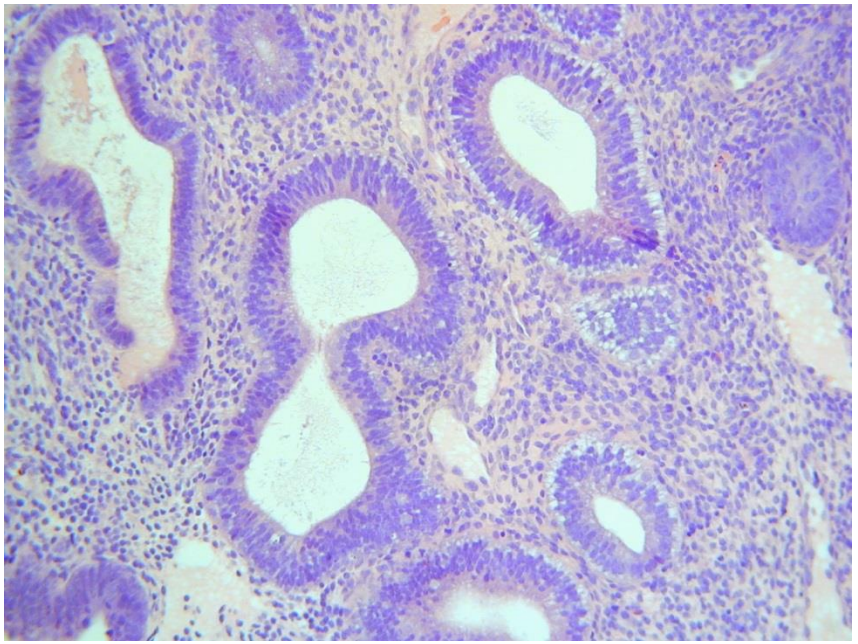
- significant glandular crowding
- proliferative activity
- cytology differs between crowded focus and background- cytologic demarcation
- usually nuclear and cytoplasmic alterations
- exclusion of benign mimics
- exclusion of carcinoma

SECRETORY HYPERPLASIA/ SECRETORY EIN

- unusual diagnosis to make
- sometimes get secretory features in hyperplasia (uncommon)
- sometimes get hyperplasia with background secretory endometrium (uncommon)- should stand out from surrounding endometrium
- tend to be younger - circulating progestogens
- may be secondary to ovulation or hormone effects in hyperplasia
- nuclear features may be “damped down” and mitoses may be low

SECRETORY FEATURES IN HYPERPLASIA



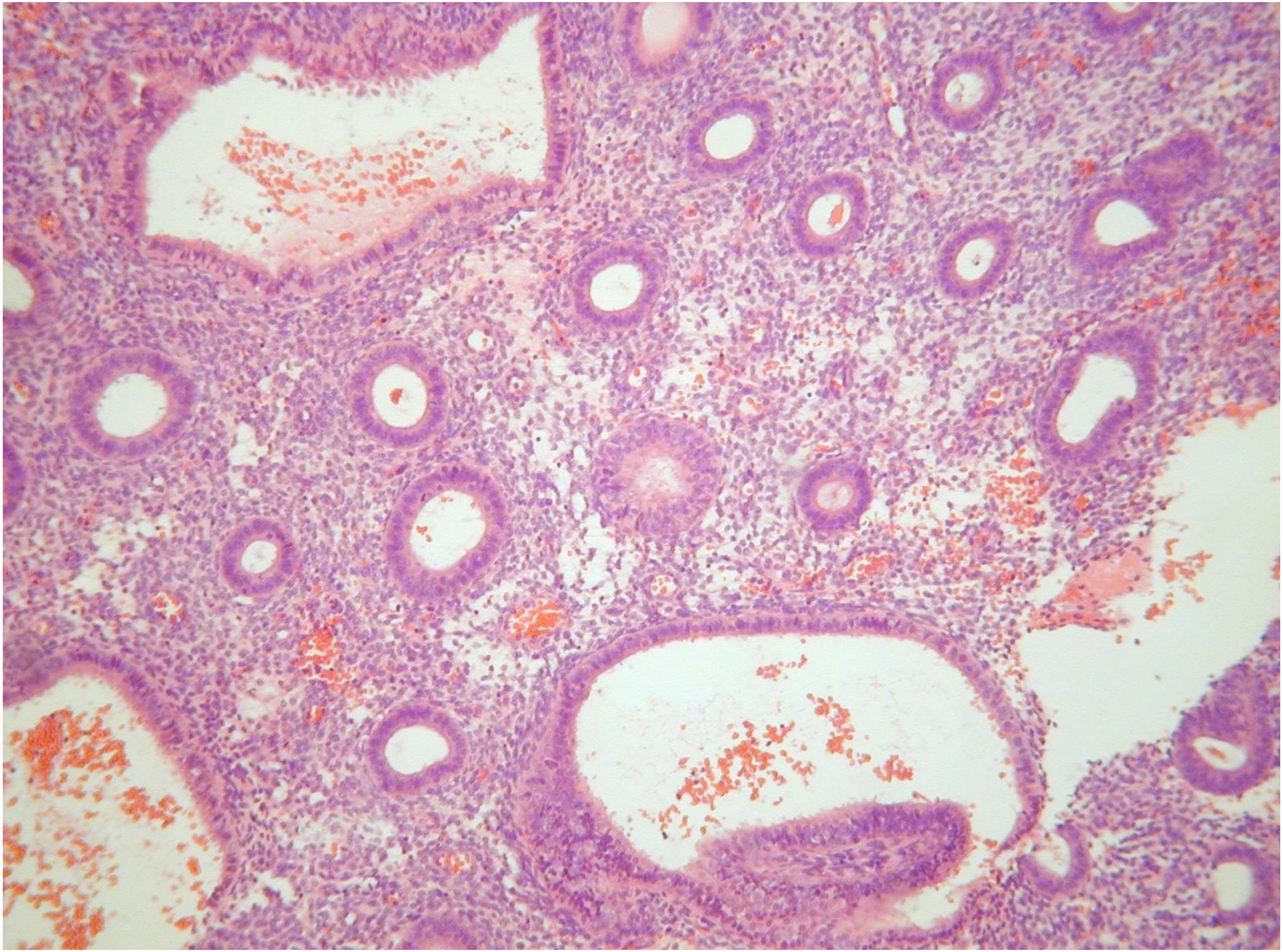


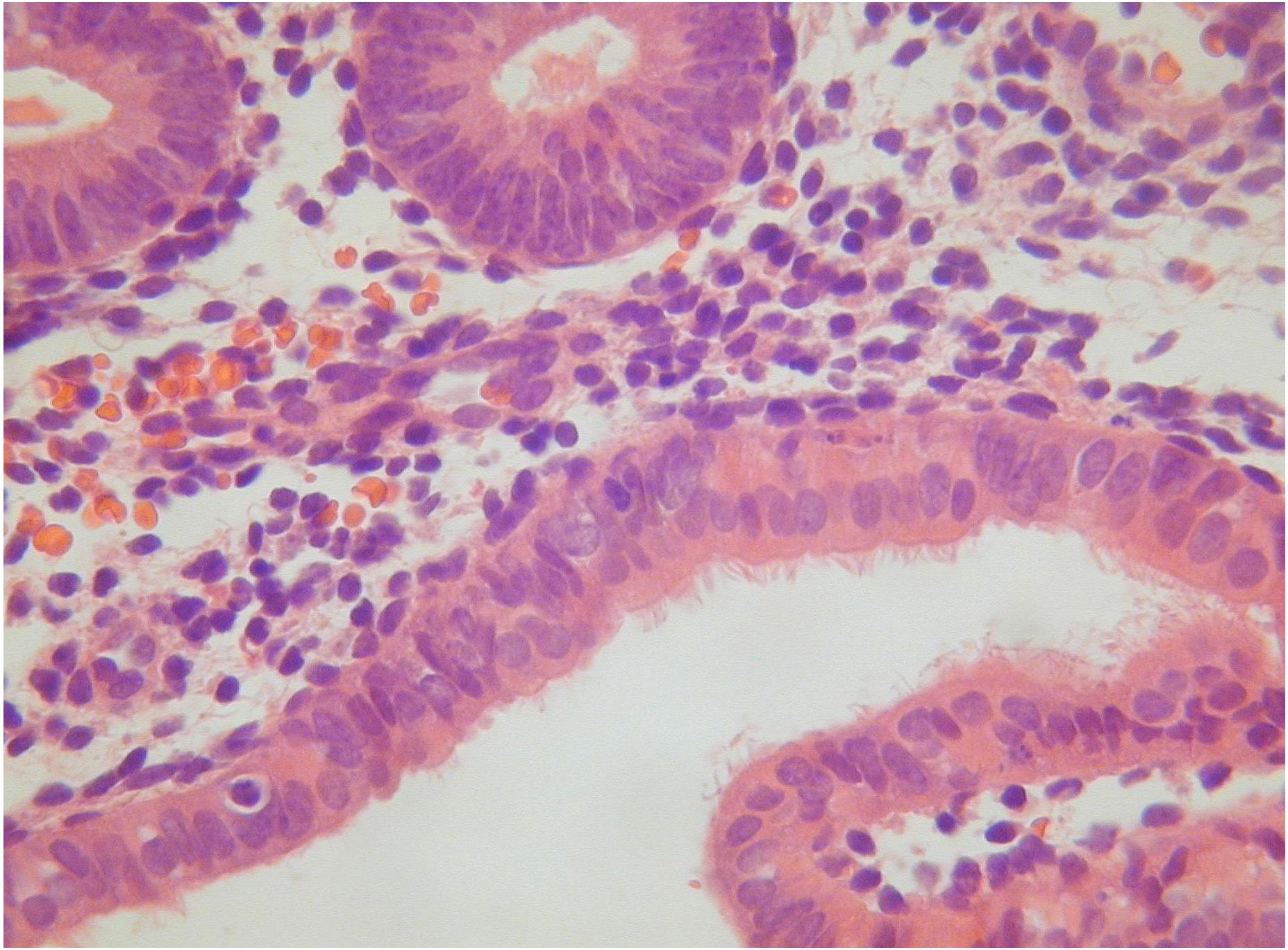
MIMICS OF HYPERPLASIA

- disordered proliferative endometrium
- artefacts (pseudopapillary/telescoping/moulding)
- secretory endometrium/Arias Stella
- cystic atrophy
- endometrial polyp
- atypical polypoid adenomyoma
- progesterone receptor modulators
- papillary proliferation of endometrium
- subtle serous carcinoma

DISORDERED PROLIFERATIVE ENDOMETRIUM (anovulatory)

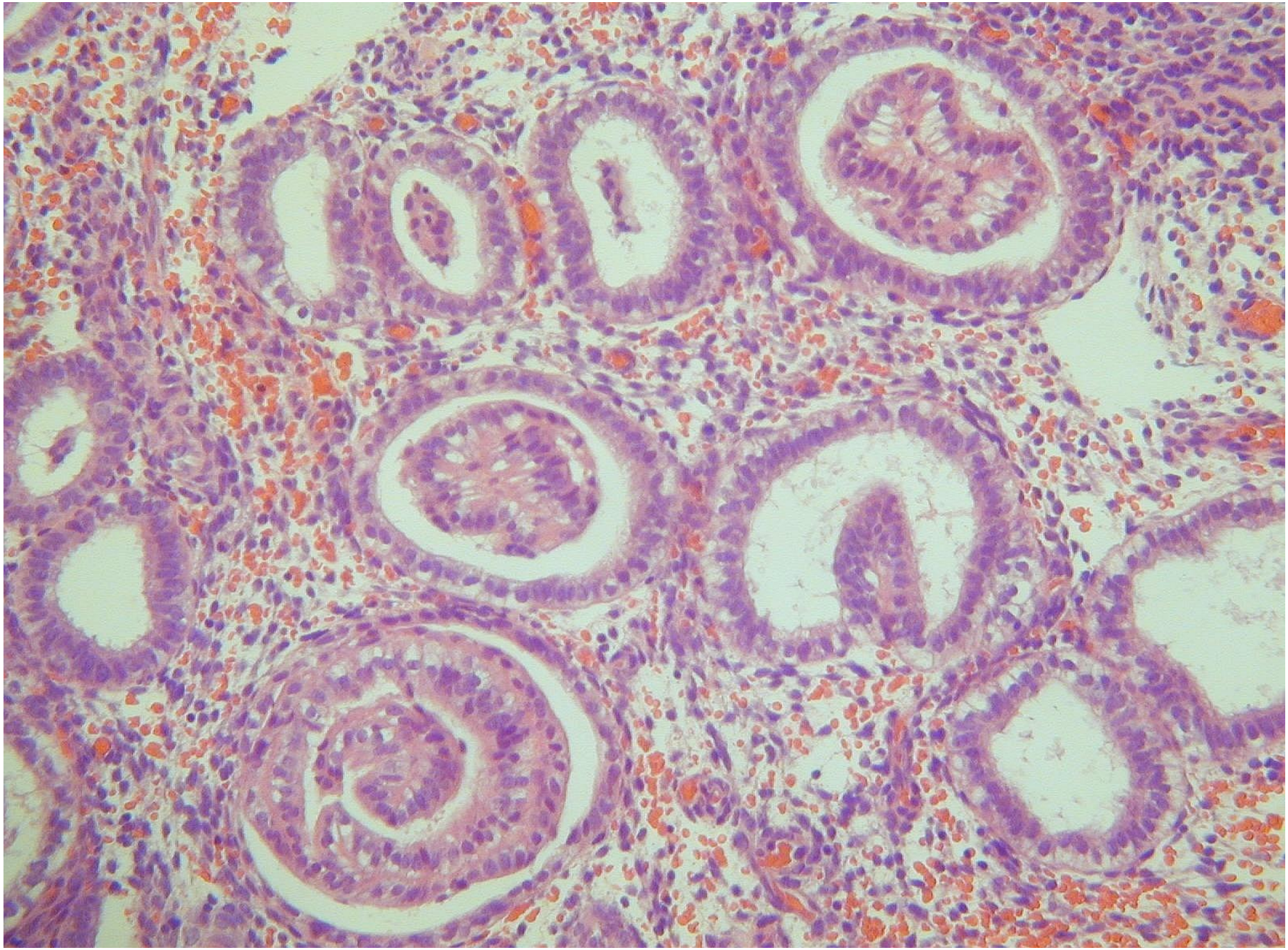
- common, especially in perimenopausal years
- response to increased oestrogenic drive without opposition of progestogen, usually secondary to anovulatory cycles
- merges with simple hyperplasia (part of same spectrum) (tend to diagnose disordered proliferative endometrium in perimenopausal years)
- occasional dilated glands with proliferative activity, stromal breakdown, metaplasias (especially ciliated)



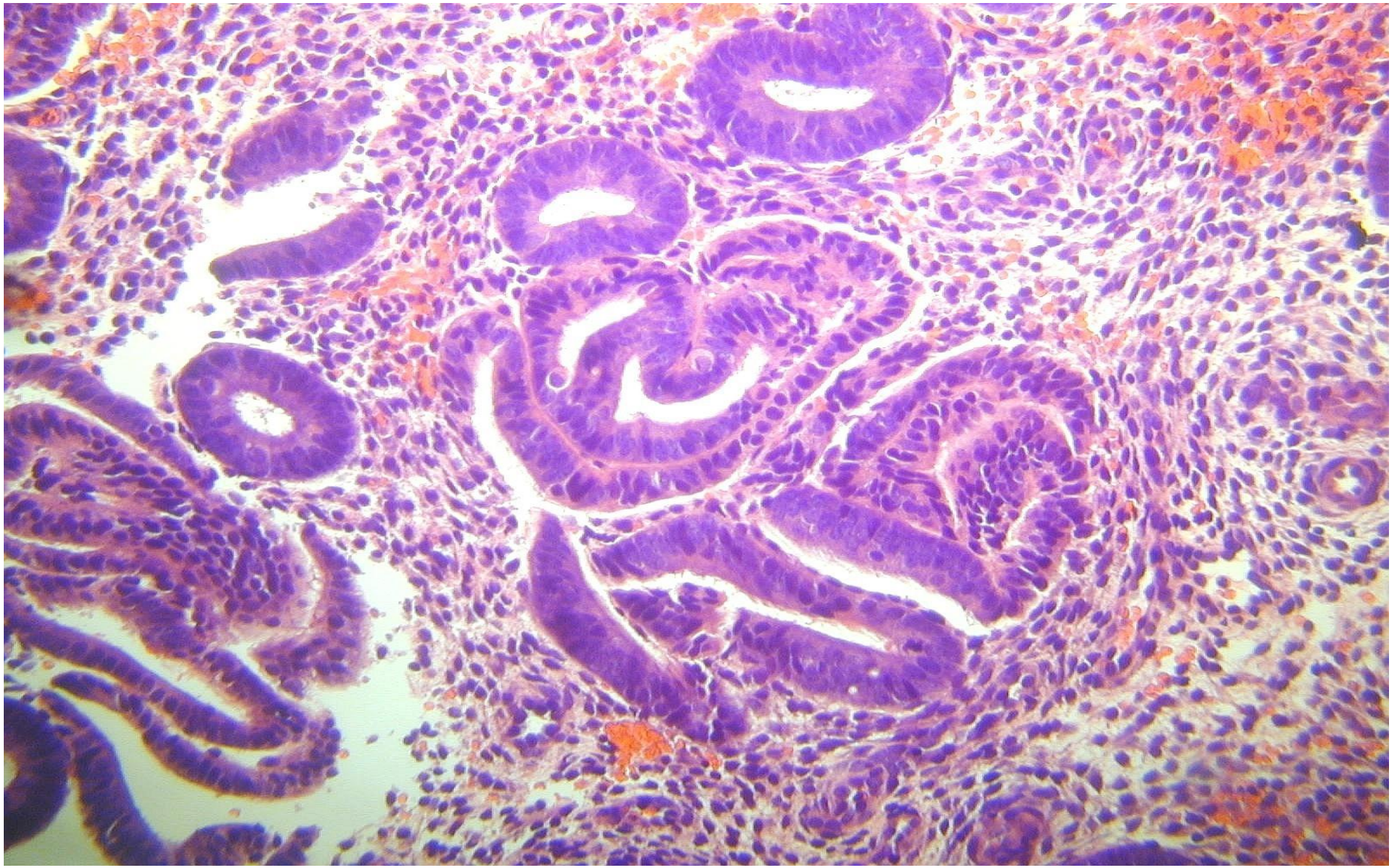


ARTEFACTS

- telescoping (glands within glands)
- glandular moulding

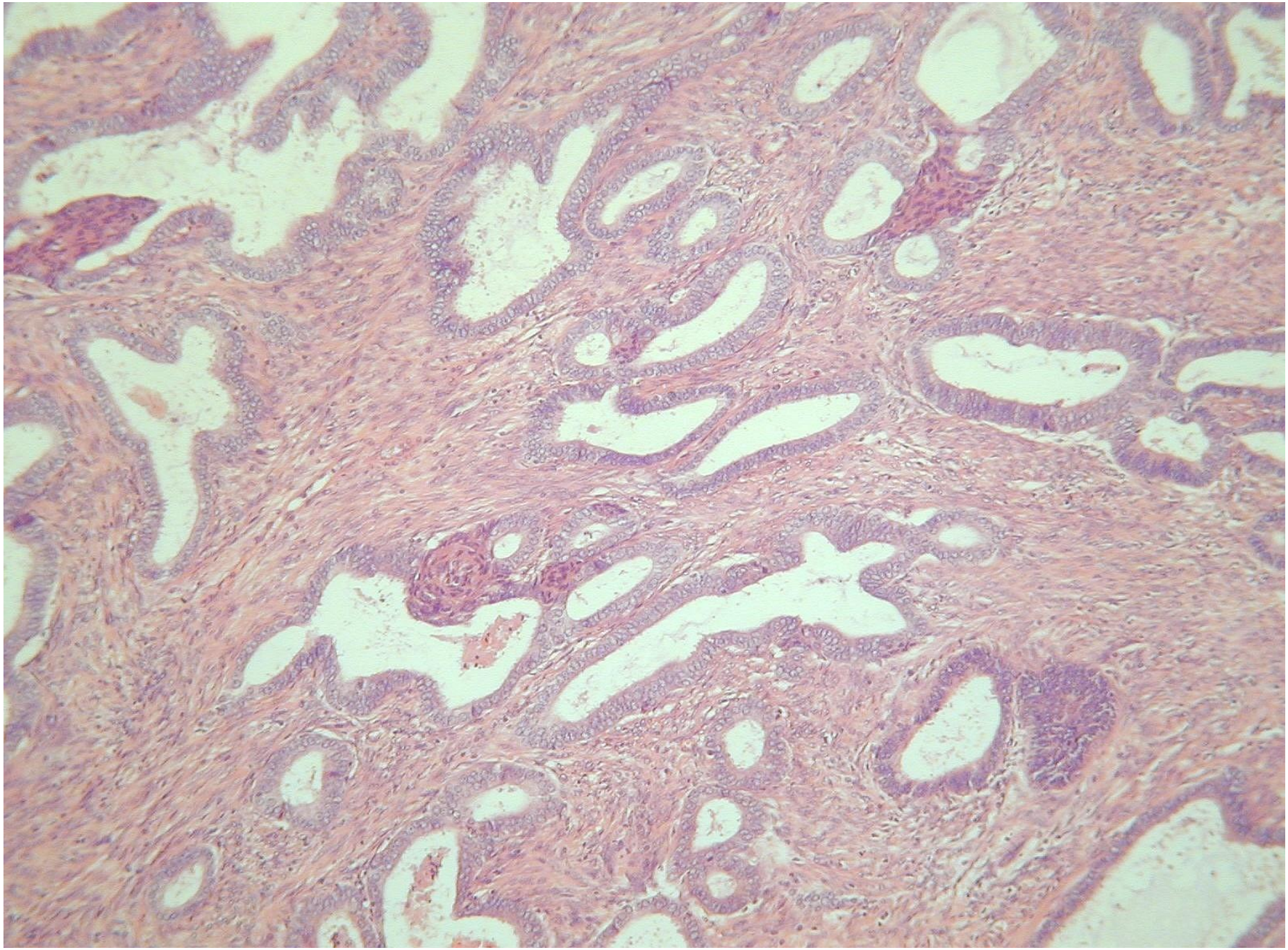


MOULDING



ATYPICAL POLYPOID ADENOMYOMA

- most common low in uterine corpus/ LUS
- endometrioid glands in myomatous or myofibromatous stroma
- differential is endometrial hyperplasia or endometrioid adenocarcinoma invading myometrium
- admixture of normal endometrium and lesion is clue
- may recur following polypectomy
- definite association with endometrioid adenocarcinoma (8.8% in one meta-analysis)
- endometrioid adenocarcinoma or AH may occur in surrounding non-polypoid endometrium
- may be areas of low grade endometrioid carcinoma within
- PROBABLY ANALAGOUS TO LOCALISED FORM OF ATYPICAL HYPERPLASIA (similar molecular alterations)



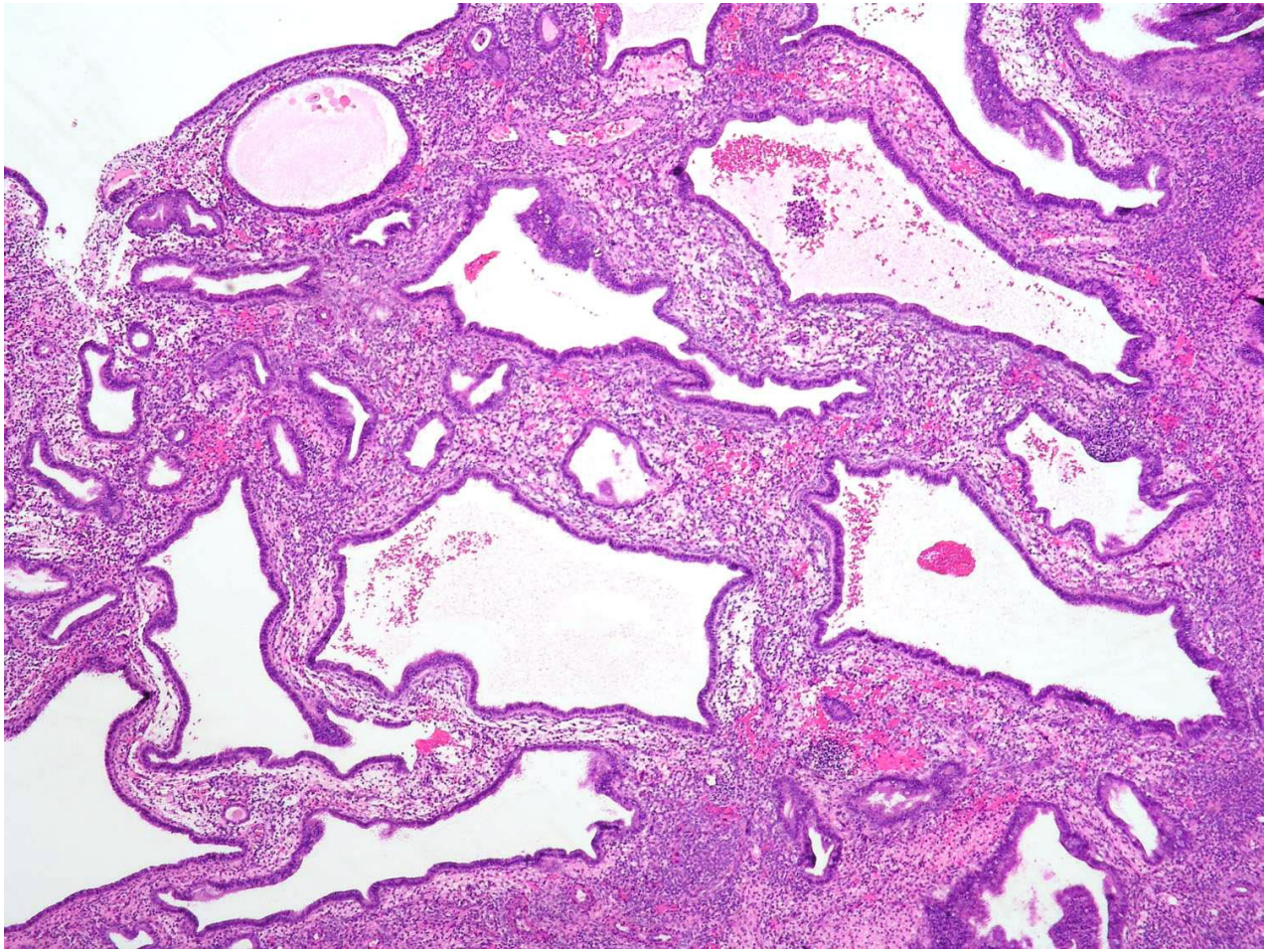
PAPER SUBMITTED FOR PUBLICATION

- PTEN mutations
- KRAS mutations
- likely beta-catenin mutations given common presence of morules

SELECTIVE PROGESTERONE RECEPTOR MODULATORS (PRMs)

- newly licensed
- ulipristal acetate (Esmya) and others
- for management of menorrhagia secondary to fibroids and endometriosis
- morphology may mimic hyperplasia- dilated glands
- tend to get unusual admixture of proliferative (mitoses) and secretory (subnuclear vacuolation) activity
- features reversible
- PAEC (PRM-associated endometrial changes)

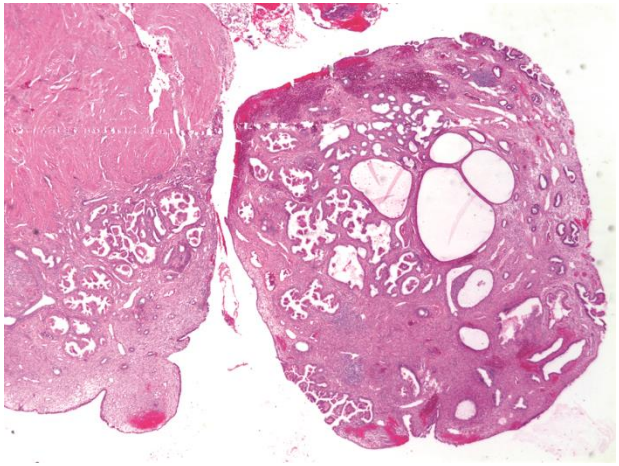
PROGESTERONE RECEPTOR MODULATORS

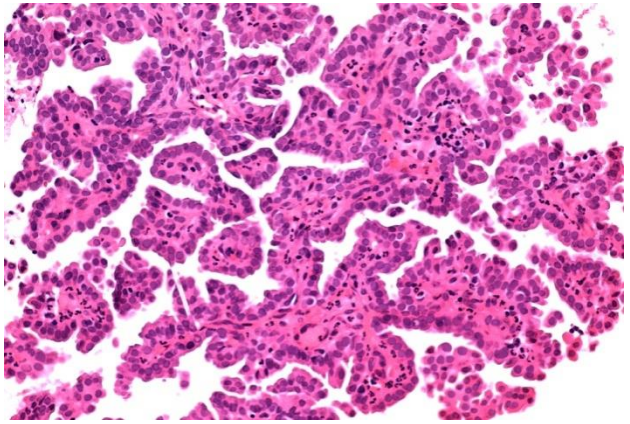


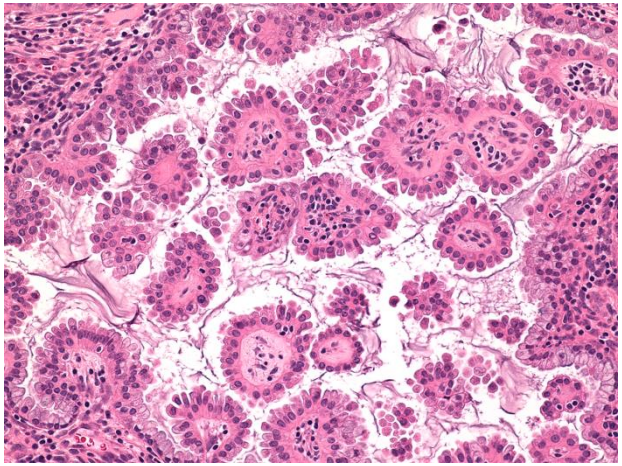
PAPILLARY PROLIFERATION OF ENDOMETRIUM

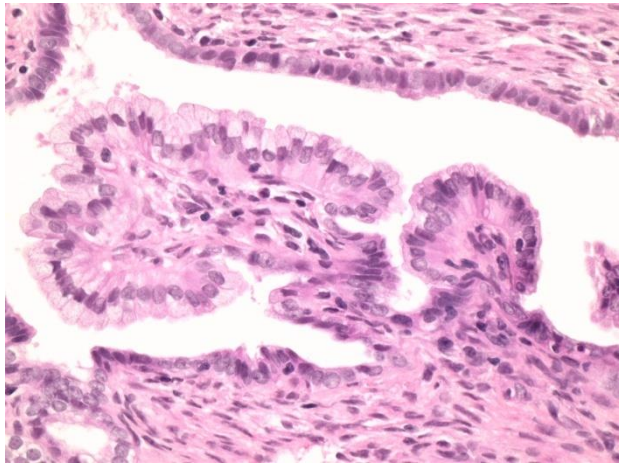
- originally described as HYPERPLASTIC PAPILLARY PROLIFERATION OF ENDOMETRIUM (Lehman and Hart)
- papillae with fibrovascular stromal cores
- bland cytology
- often associated with epithelial cytoplasmic change (metaplasia), especially mucinous
- most common within and on surface of polyps
- may be misdiagnosed as hyperplasia or architecturally well differentiated adenocarcinoma
- usually benign outcome (but occasionally associated with hyperplasia or carcinoma)

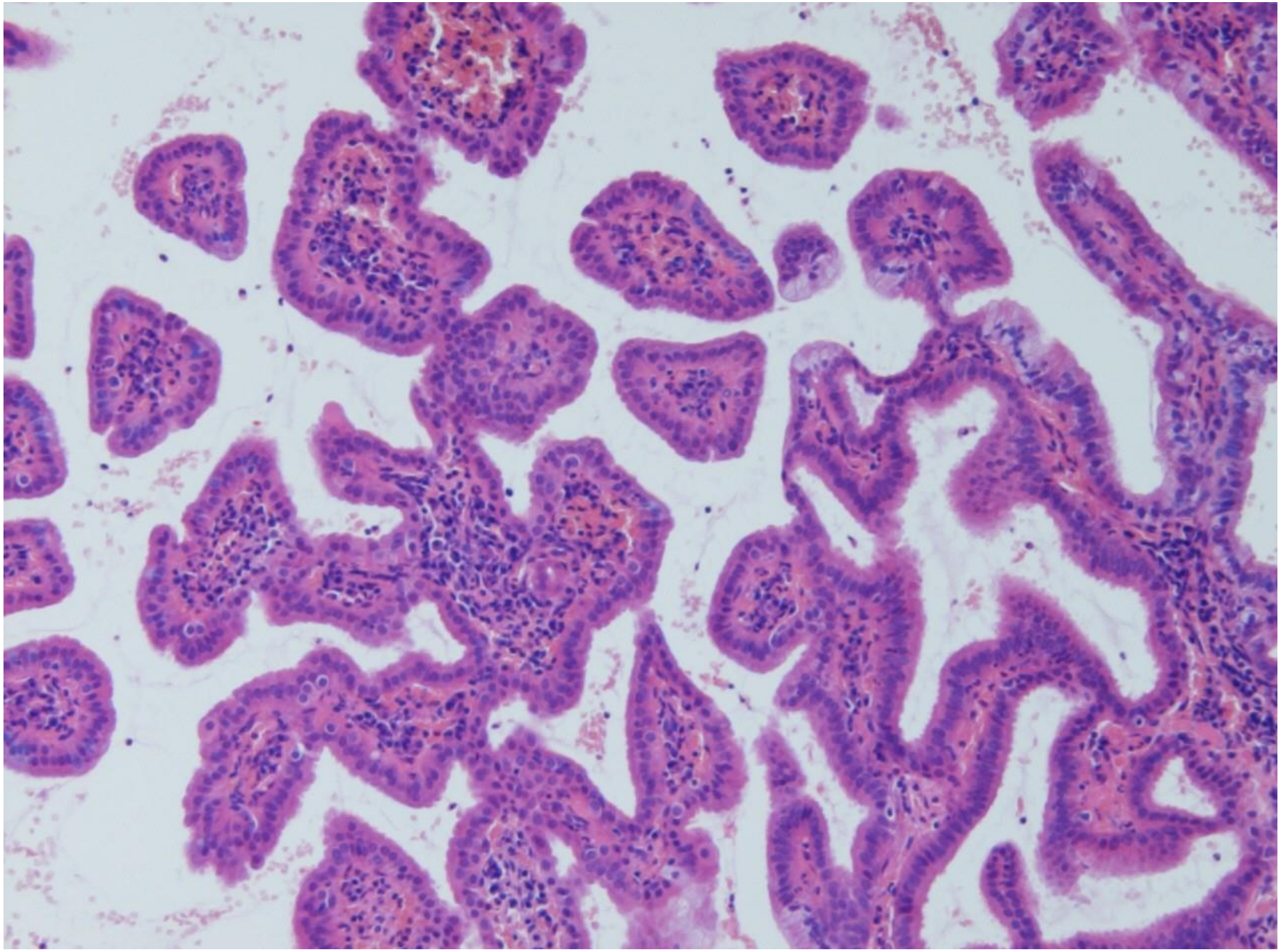
PAPILLARY PROLIFERATION OF ENDOMETRIUM

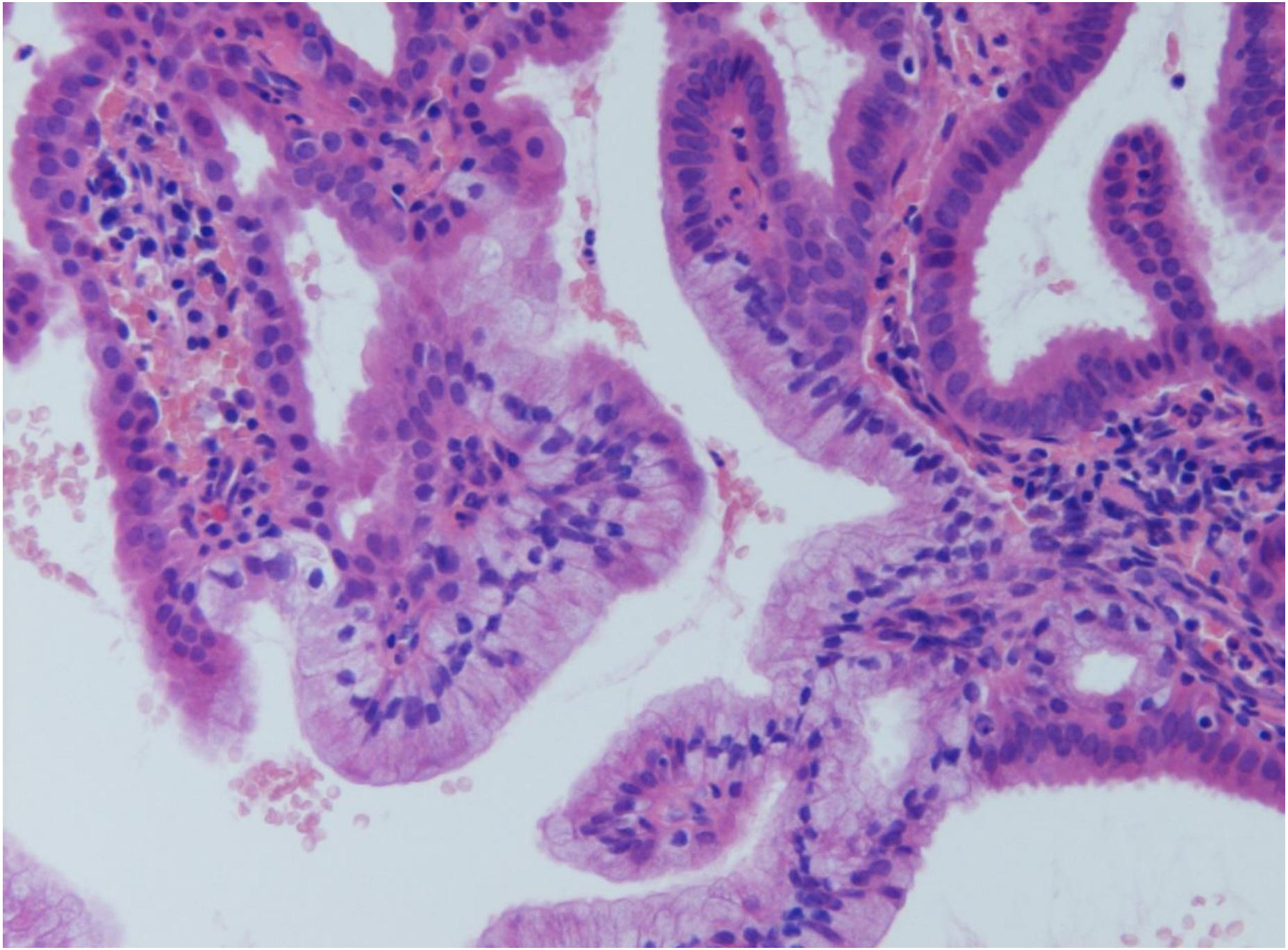






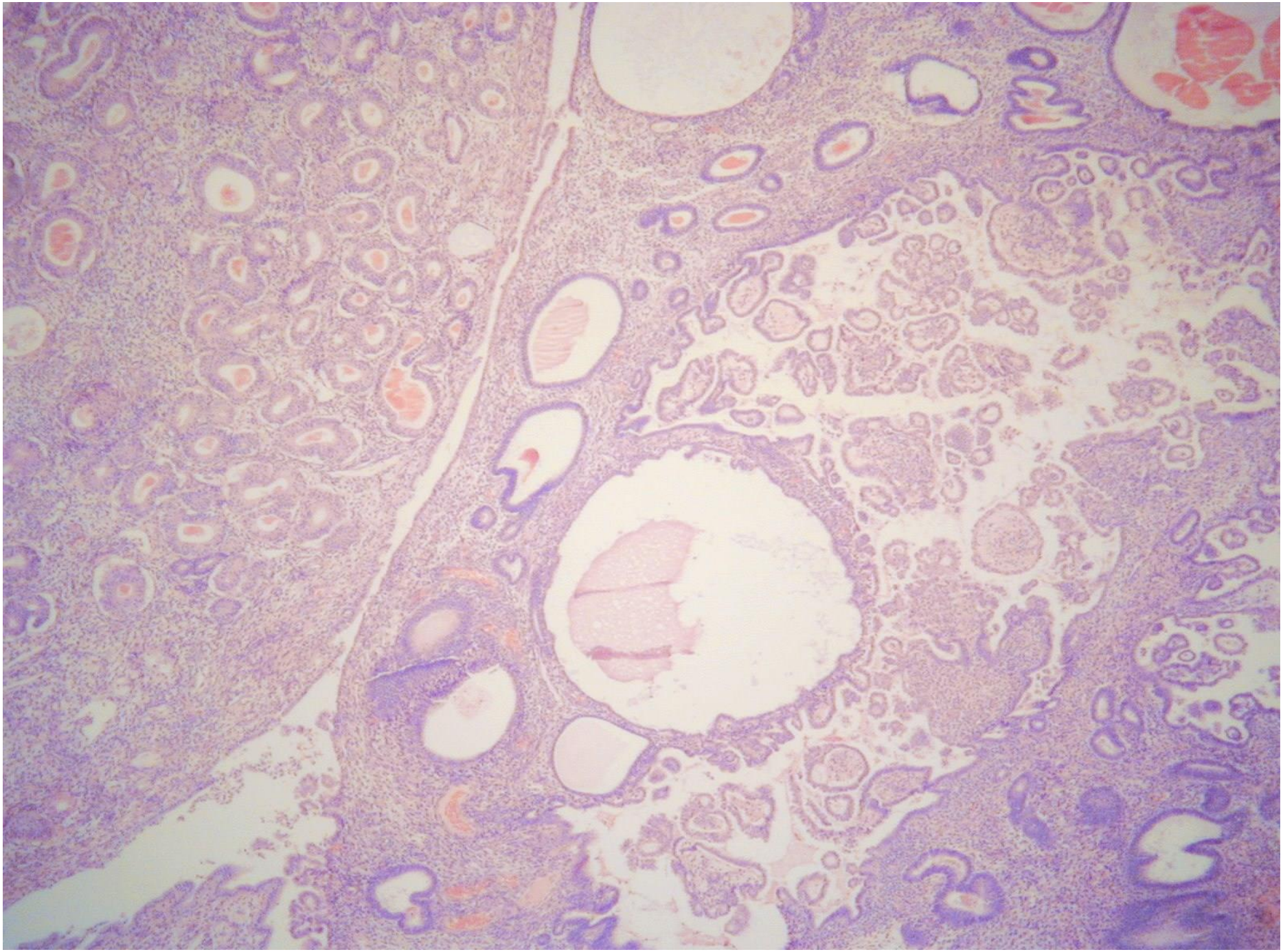






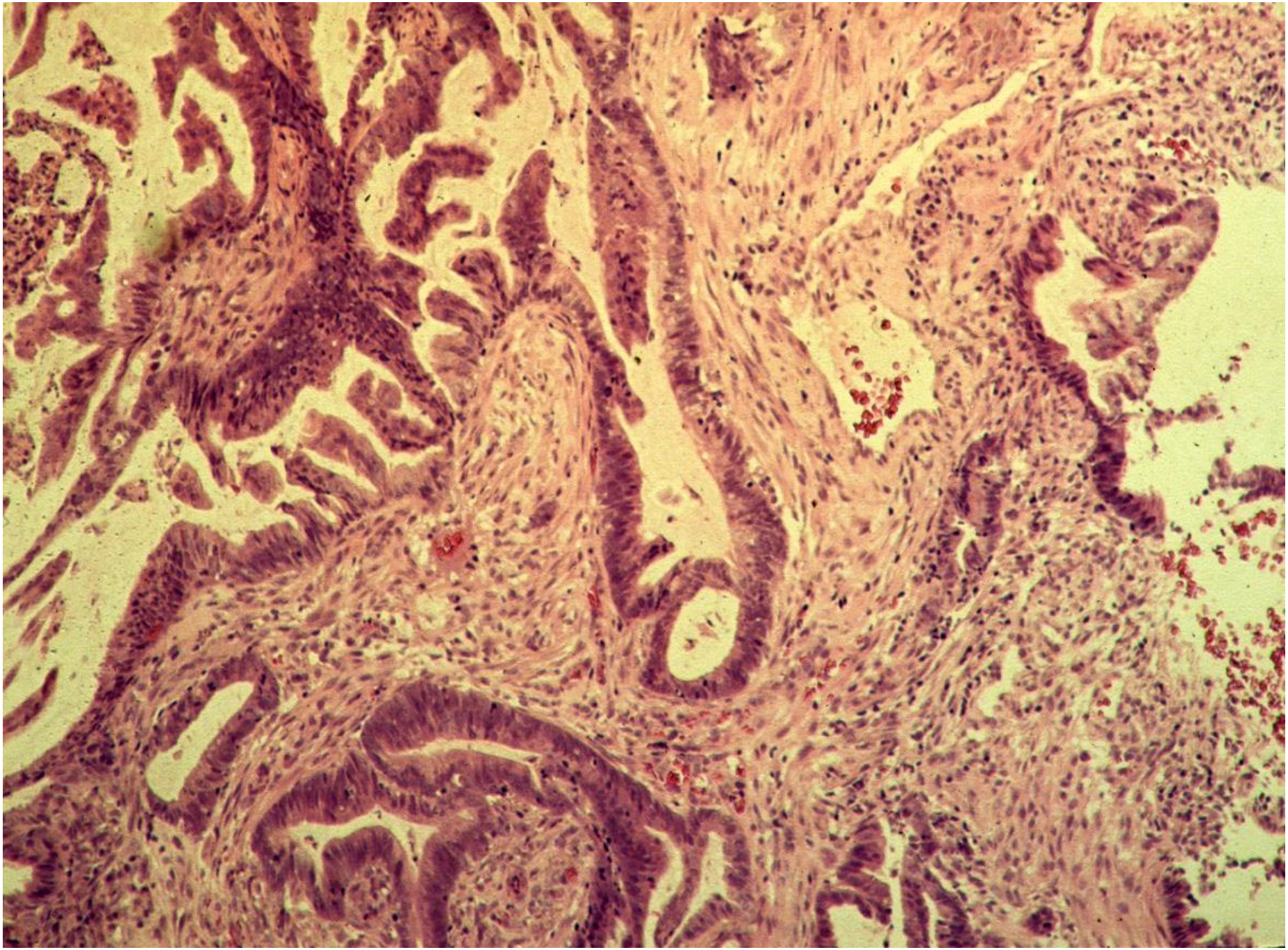
AJSP 2013;37;167-177

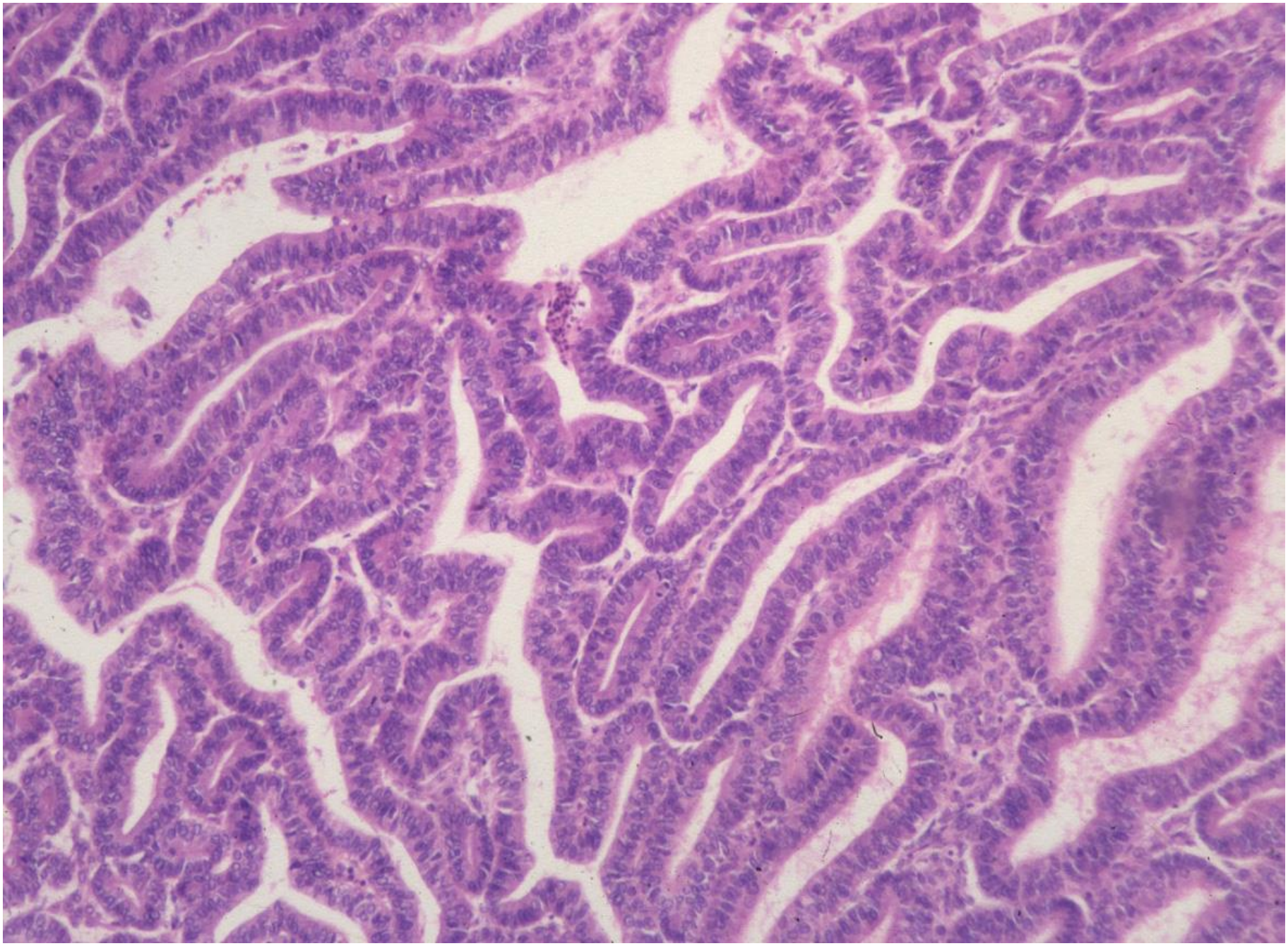
- 59 cases of papillary proliferation of endometrium (PPE) (no cytologic atypia)
- group 1- simple/focal papillae; group 2- complex/widespread papillae
- 80% had endometrial polyp (66% involved by PPE)
- 90% had epithelial metaplasia- most commonly mucinous
- coexistent or subsequent non-atypical or atypical hyperplasia found in 17% and 13% respectively
- 13% had low grade endometrioid adenocarcinoma, either concurrently or subsequently
- group 2 significantly associated with premalignant or malignant change
- **simple papillae- benign- term benign PPE appropriate**
- **complex or widespread papillae- require follow up- analogous to atypical hyperplasia- complex PPE**
- may be difficult to distinguish between group 1 and 2 on small biopsy specimen (artificial separation)

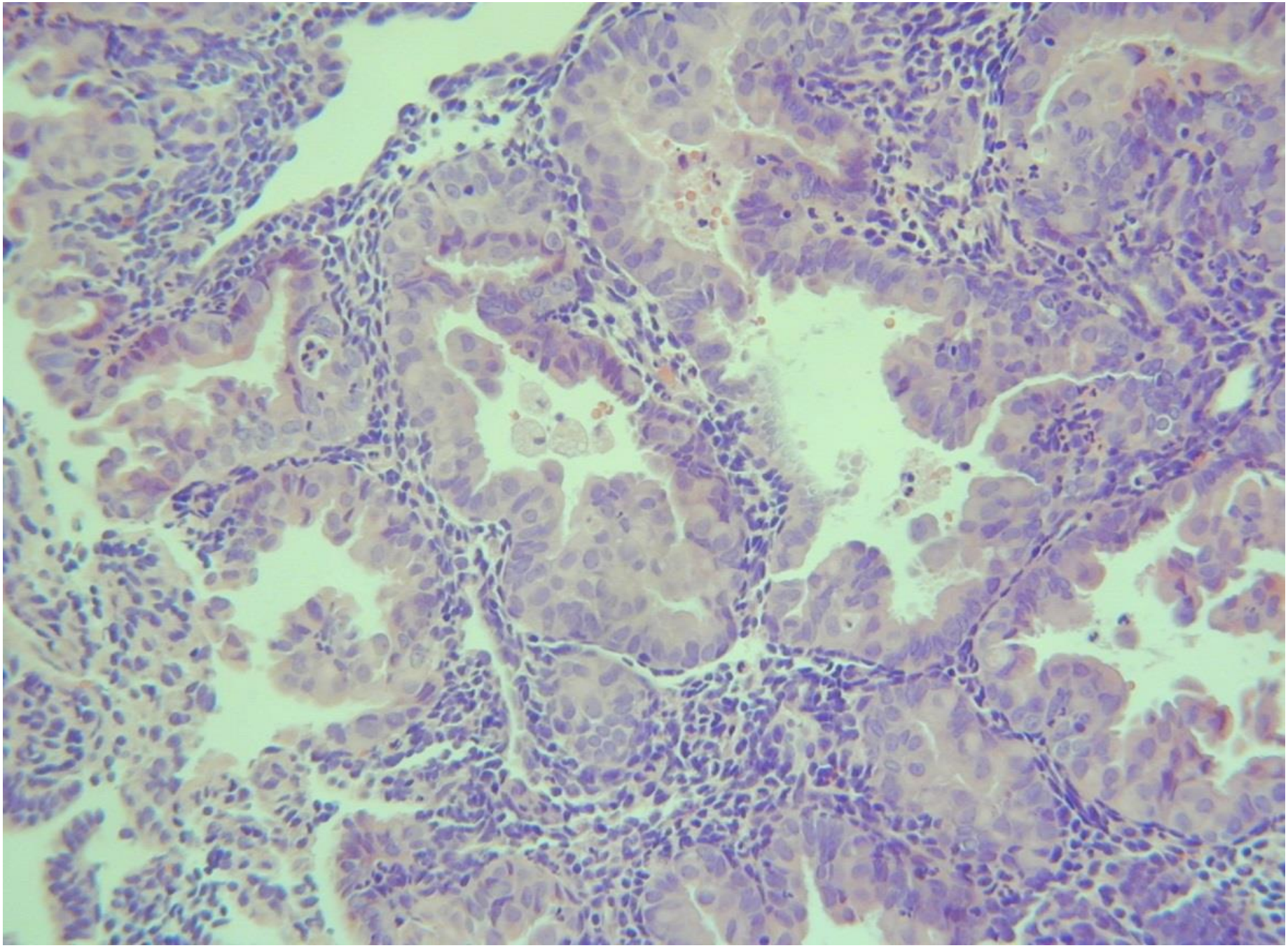


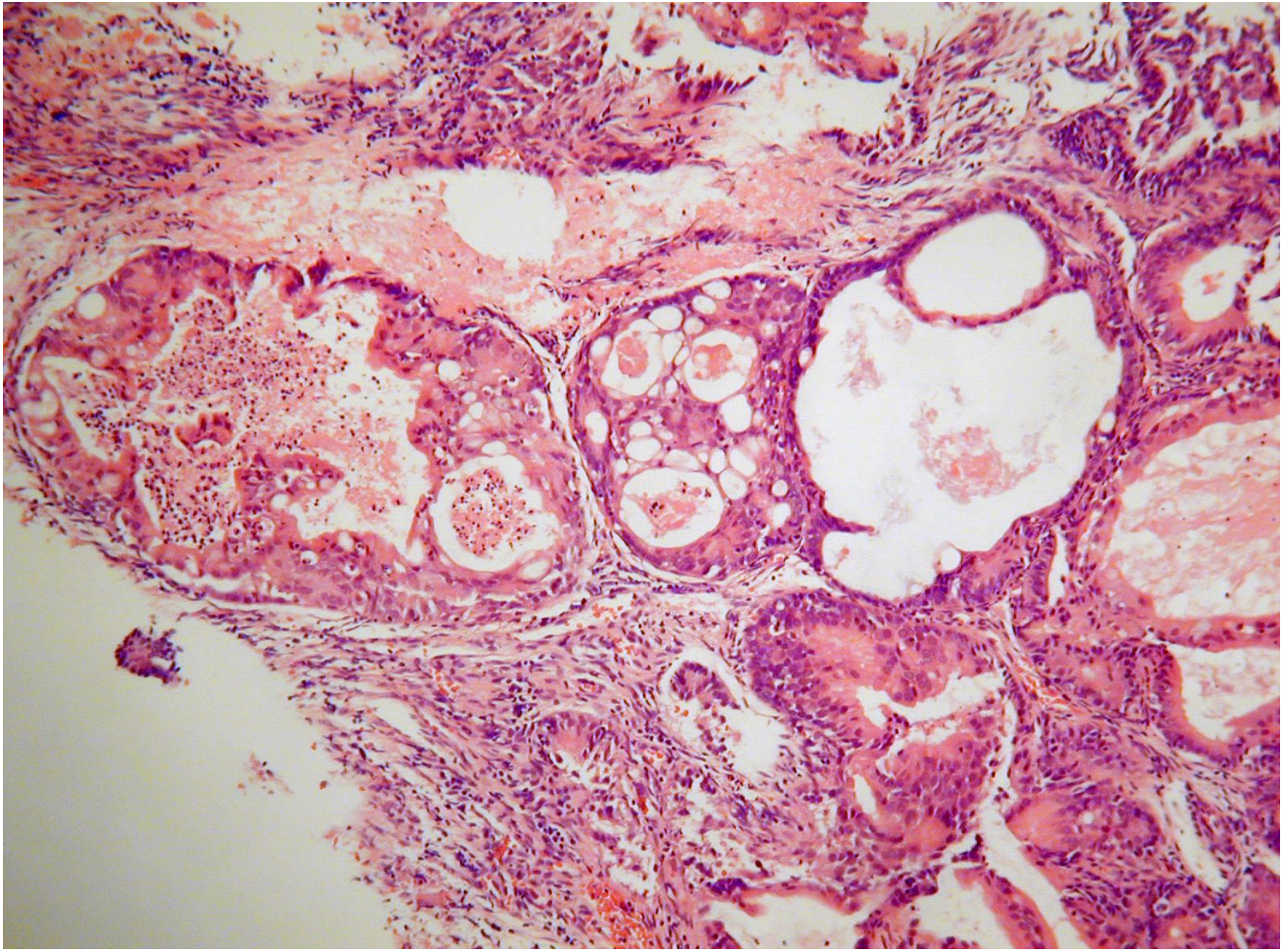
Distinction Between Atypical Hyperplasia and Endometrioid Carcinoma

- studies show high risk of endometrioid carcinoma in hysterectomy following diagnosis of atypical hyperplasia (undersampling or UNDERDIAGNOSIS)
- some have suggested size limit for diagnosis of carcinoma (2.1mm)
- complete stromal exclusion (back to back glands) suggests carcinoma
- cribriform architecture suggests carcinoma
- papillary or micropapillary architecture suggests carcinoma (IF SEE SIGNIFICANT PAPILLARY ELEMENTS, PROBABLY NOT A HYPERPLASIA- can get small intraglandular micropapillae)
- labyrnthine/ “maze-like” architecture suggests carcinoma
- necrotic debris within glands suggests carcinoma
- desmoplastic stroma in keeping with carcinoma (uncommon to see in endometrial biopsy)



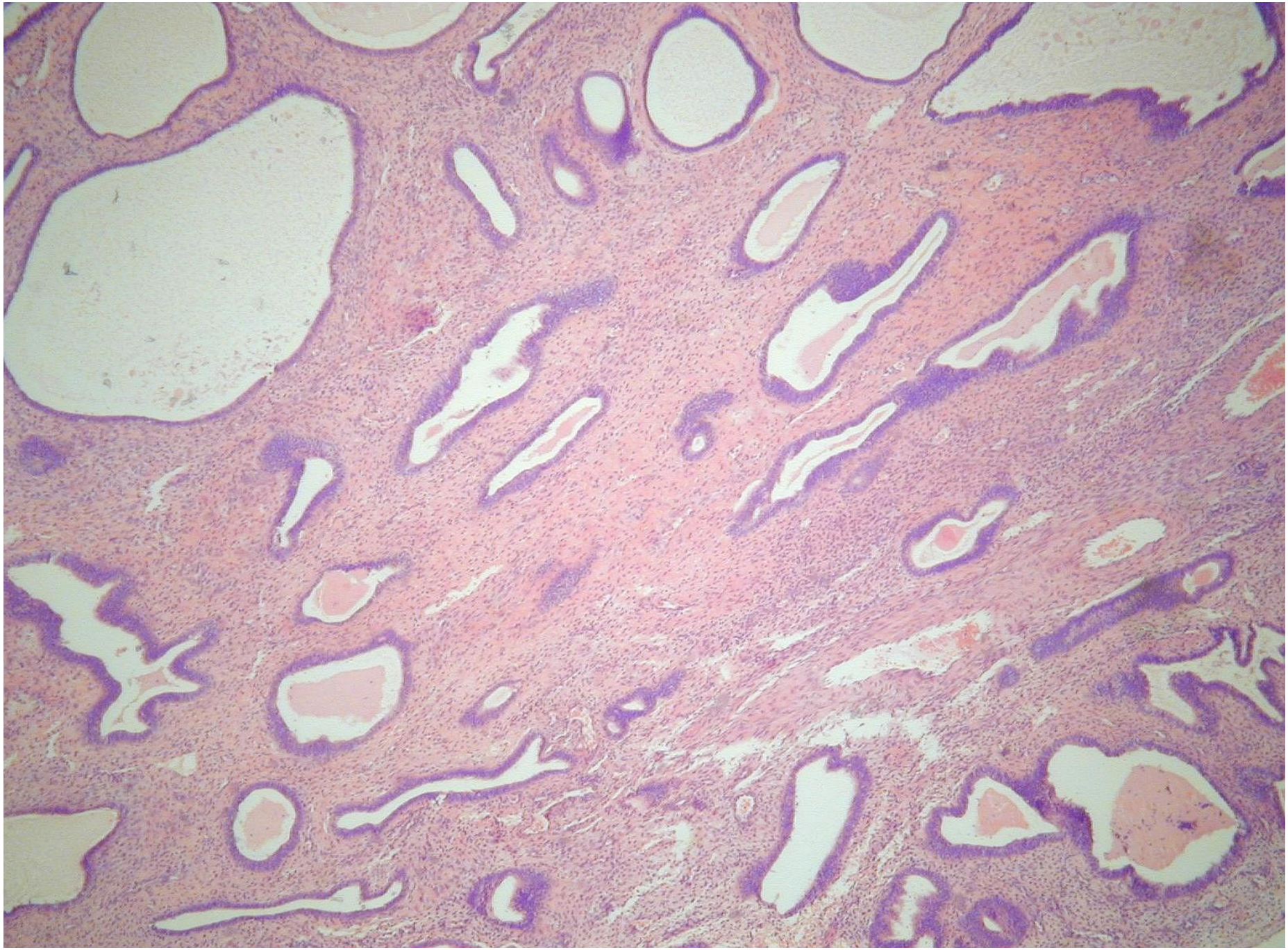


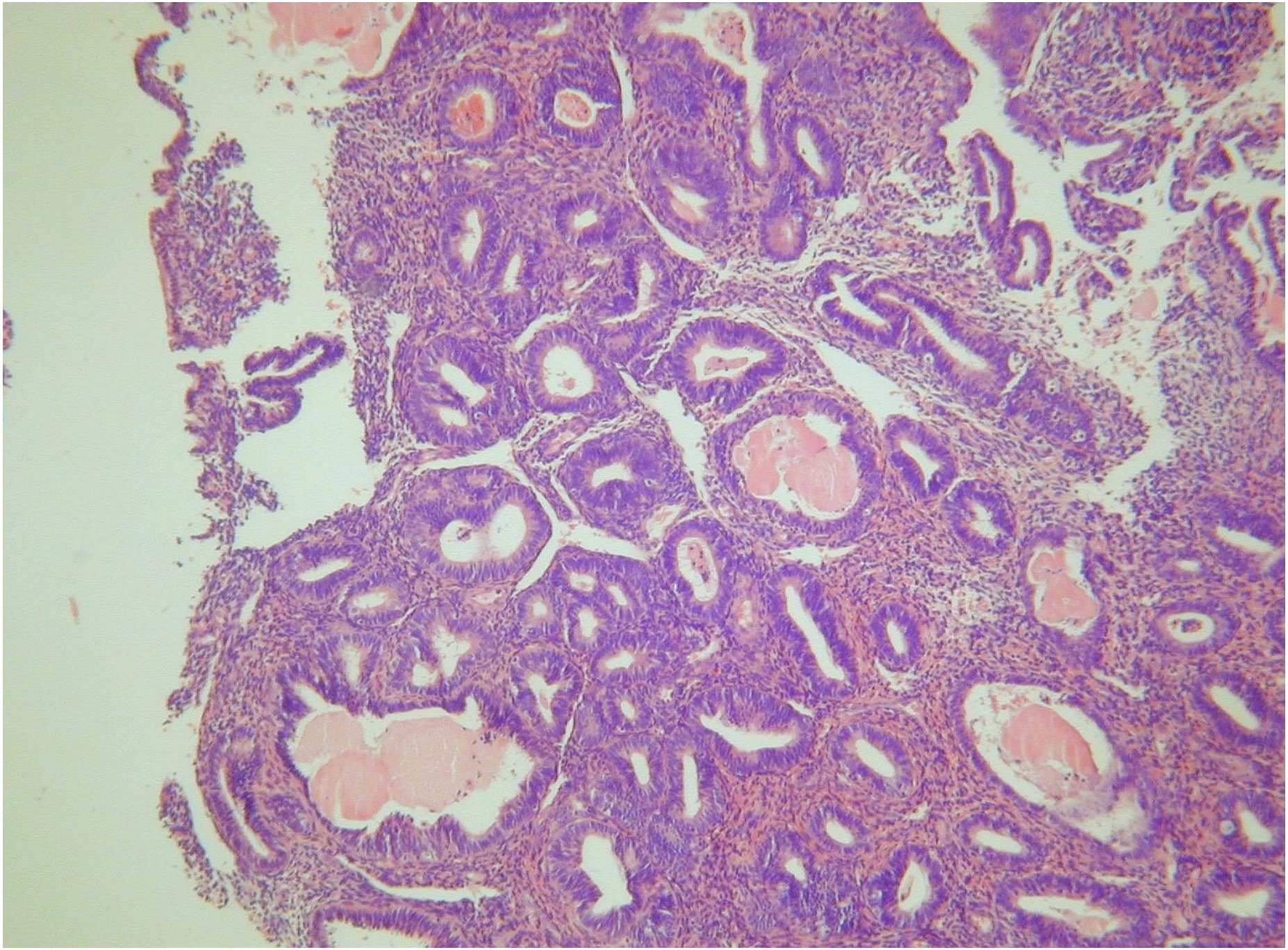


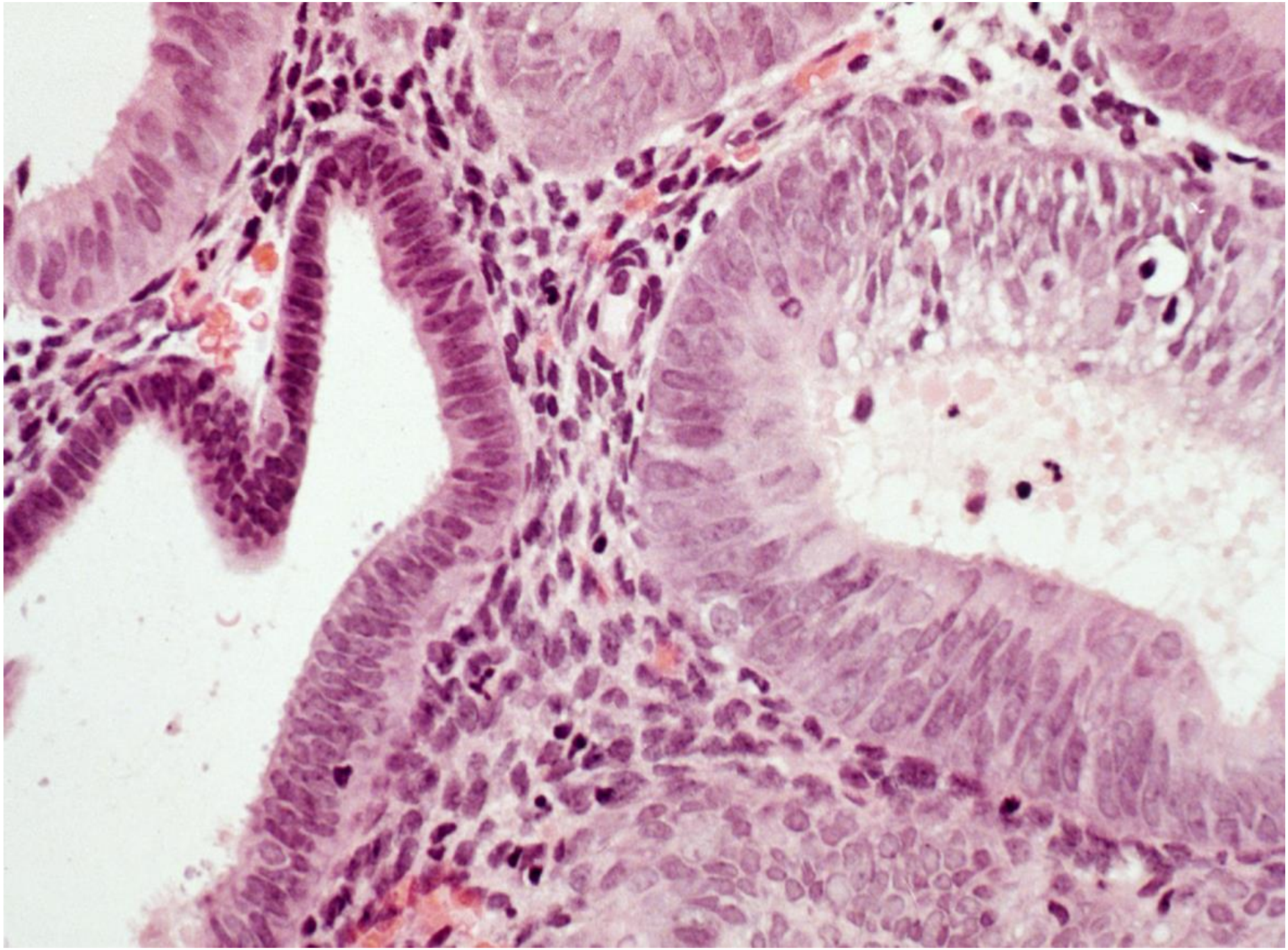


ENDOMETRIAL HYPERPLASIA IN POLYP

- not uncommon for hyperplasia to be identified in endometrial polyp
- don’t diagnose simple hyperplasia in polyp
- diagnose complex hyperplasia (hyperplasia without atypia) or atypical hyperplasia using same criteria as in non-polypoid endometrium
- ? significance of hyperplasia in polyp
- endometrial polyps more common in patients with atypical hyperplasia/EIN







ENDOMETRIAL HYPERPLASIA IN POLYP

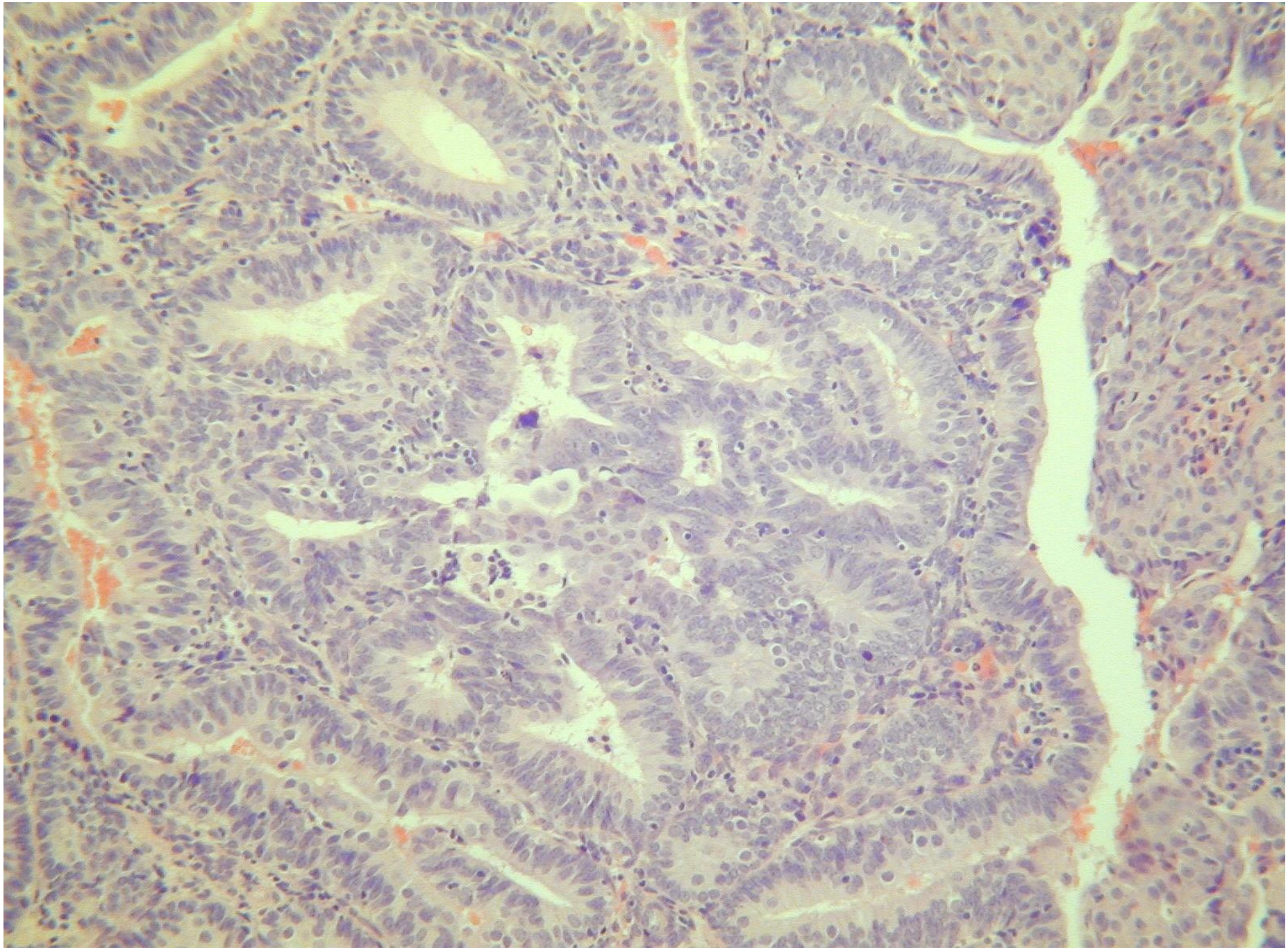
- little information in literature
- BJOG 2007;114;944-950
- in about 50% of cases, hyperplasia will involve non-polypoid endometrium

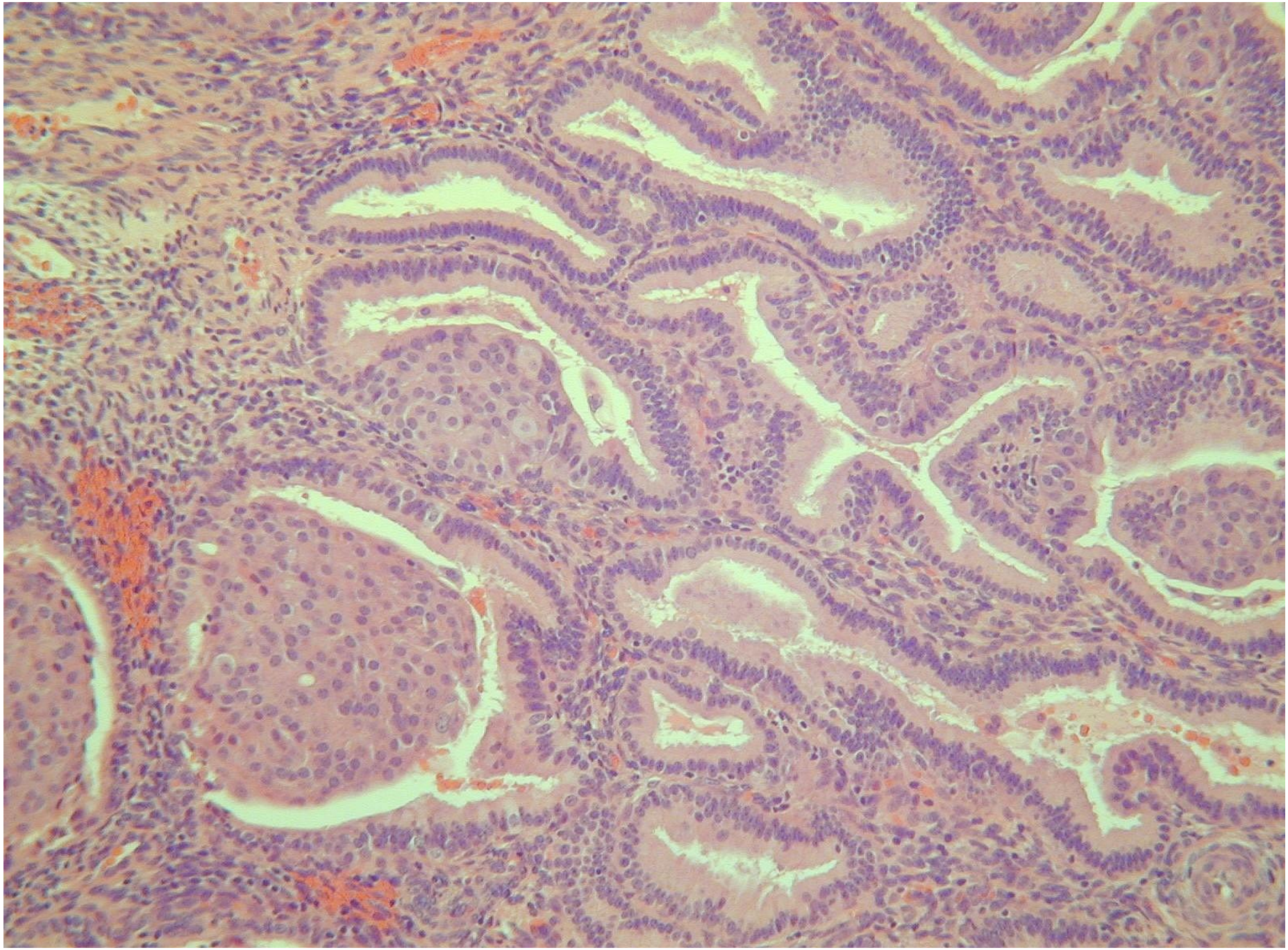
PROGESTIN TREATMENT OF ATYPICAL HYPERPLASIA OR ENDOMETRIOID CARCINOMA

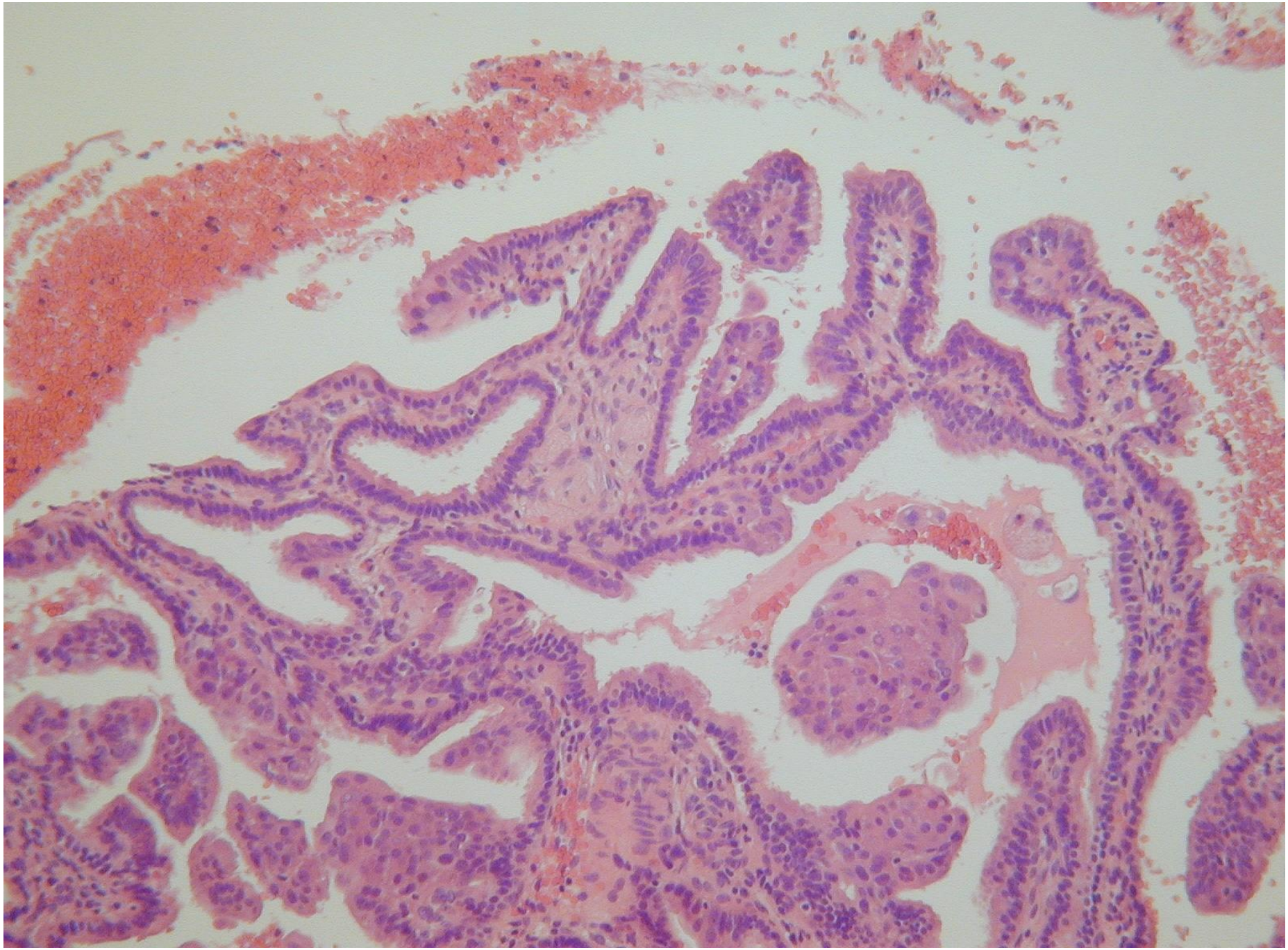
- occasionally used in management of low grade endometrioid adenocarcinoma or atypical hyperplasia
- usually when fertility preservation is an issue or poor operative risk
- oral progestogens or IUD or both
- perform MRI to try to exclude myoinvasive disease
- reasonable response rate but risk of recurrence
- need regular endometrial biopsies (probably should take off progestogens)
- need to stay on progestogens for some time

CASE

- diagnosis- mixture of atypical hyperplasia and grade 1 endometrioid adenocarcinoma
- treated with progestogens for 3 months
- further biopsy

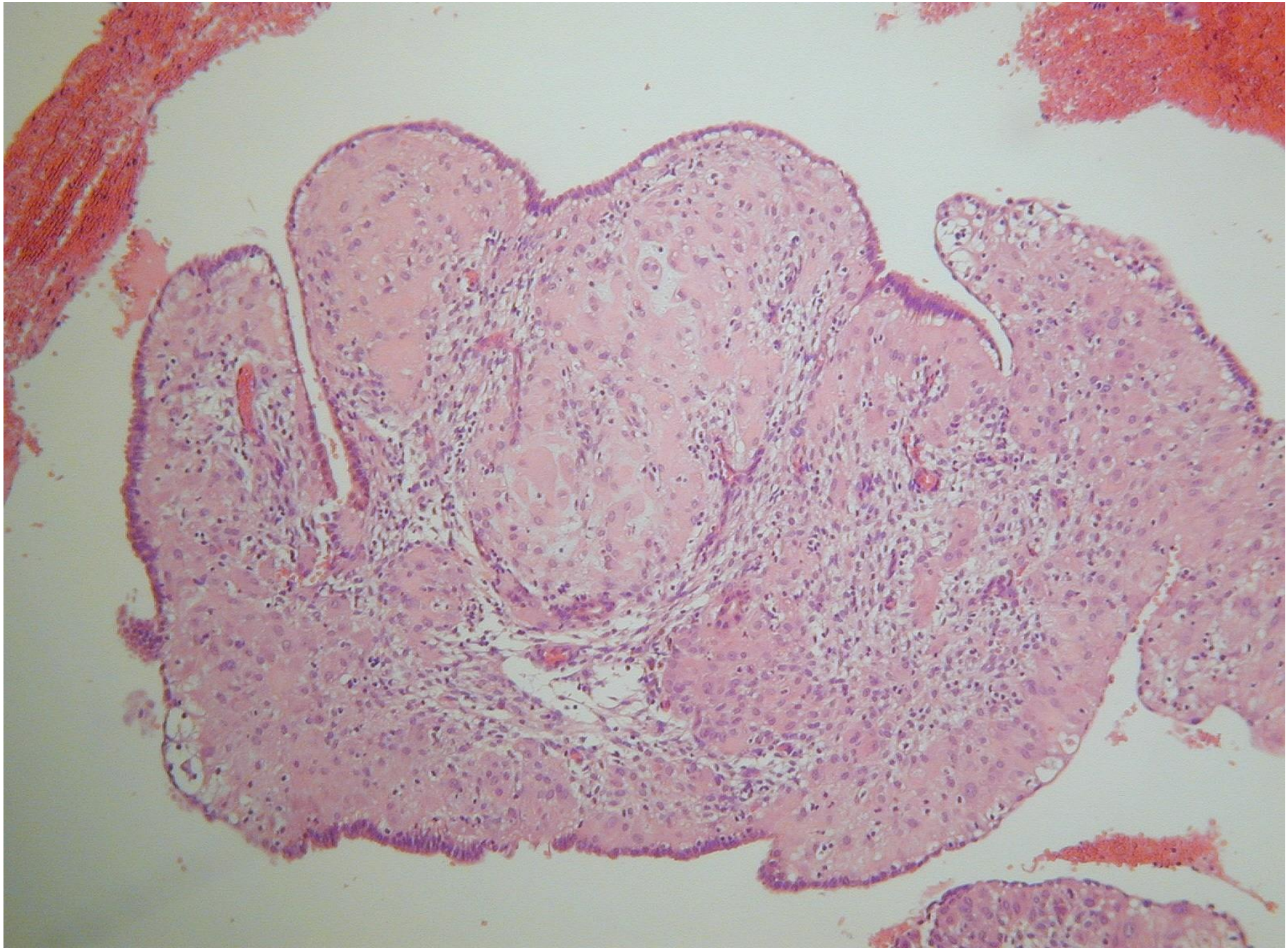






CASE

- treated with progestogens for further 6 months
- further biopsy



ALTERATIONS INDUCED BY PROGESTOGENS

- decreased gland to stroma ratio
- decreased cytologic atypia
- decreased mitotic activity
- increased cytoplasmic eosinophilia
- epithelial metaplasias/ cytoplasmic changes
- stromal decidualisation/pseudo-decidualisation (mainly in benign endometrium)
- ? increased papillary and cribriform architecture
- downregulation of ER, PR, Ki-67, bcl2

INTERPRETATION DIFFICULT

- ? hyperplasia, ? responding hyperplasia
- must report in knowledge of prior biopsy
- useful to look at prior biopsy when reporting
- difficulties if no prior biopsy
- probably should take off progestogens before biopsy

ENDOMETR**IAL/OID** INTRAEPITHELIAL NEOPLASIA (EIN)

- suggested terminology for precursor lesions of endometrioid adenocarcinoma - George Mutter and colleagues
- used in a few major centres in USA but not in widespread use (probably not likely to be)
- WHO- acceptable synonym to atypical hyperplasia
- useful in focusing pathologists on important criteria

ENDOMETRIOID INTRAEPITHELIAL NEOPLASIA (EIN)

- criteria developed by correlation of morphological, clinical, morphometric and molecular (monoclonal- PTEN, PAX 2-ve, same molecular alterations as subsequent carcinoma) parameters

- diagnose EIN using morphology

CRITERIA FOR EIN (need all)

- area of glands exceeds that of stroma (VPS <55%)- more glands than stroma
- cytology differs between crowded focus and background - cytologic demarcation
- maximum linear dimension exceeds 1mm
- exclusion of benign mimics
- exclusion of carcinoma

MAIN DIFFERENCE BETWEEN EIN AND ATYPICAL HYPERPLASIA

- don’t require nuclear atypia (subjective)
- based on cytologic demarcation
- size criteria (1 mm)

WHAT IF LESS THAN 1mm?

- subdiagnostic of EIN (<1mm; glands less than stroma; others)
- recommend repeat biopsy 3-6 months
- 77% benign, 19% EIN, 4% cancer

CORRELATION WITH WHO

- simple hyperplasia - hyperplasia without atypia
- complex hyperplasia (most) –hyperplasia without atypia
- complex hyperplasia (minority) – EIN
- atypical hyperplasia – most are EIN

ADVANTAGES OF EIN

- good outcome data
- more predictive of endometrioid adenocarcinoma development than WHO
- 45 fold increased likelihood of endometrioid adenocarcinoma compared with hyperplasia without atypia
- correlates well with molecular alterations
- does away with subjective assessment of nuclear atypia

DISADVANTAGES OF EIN

- in many ways just renaming AH
- new classification will be unfamiliar to clinicians and pathologists
- requires retraining of pathologists
- endometrial metaplasias (if significantly crowded has to be atypical hyperplasia)
- ALL/MOST PAPERS FROM 1 GROUP

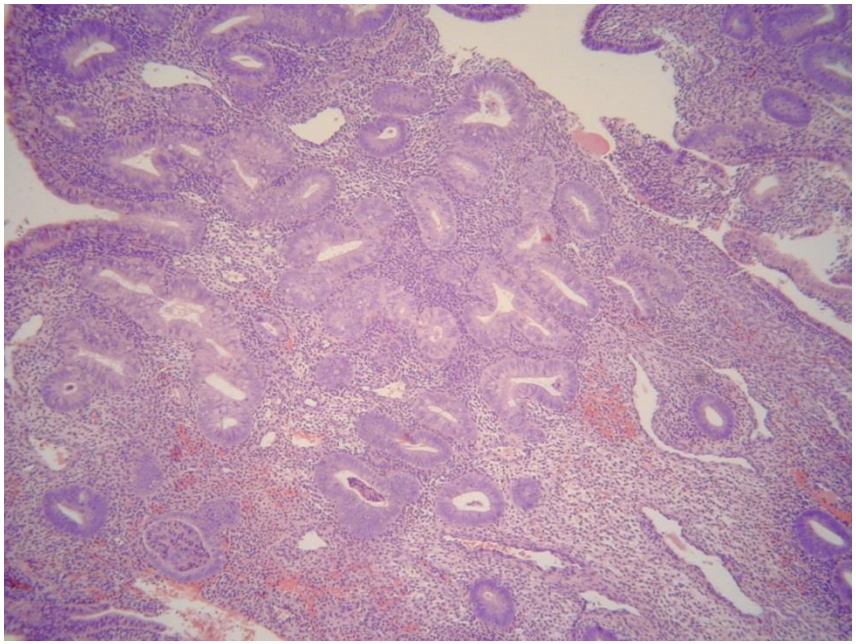
EPITHELIAL METAPLASIAS

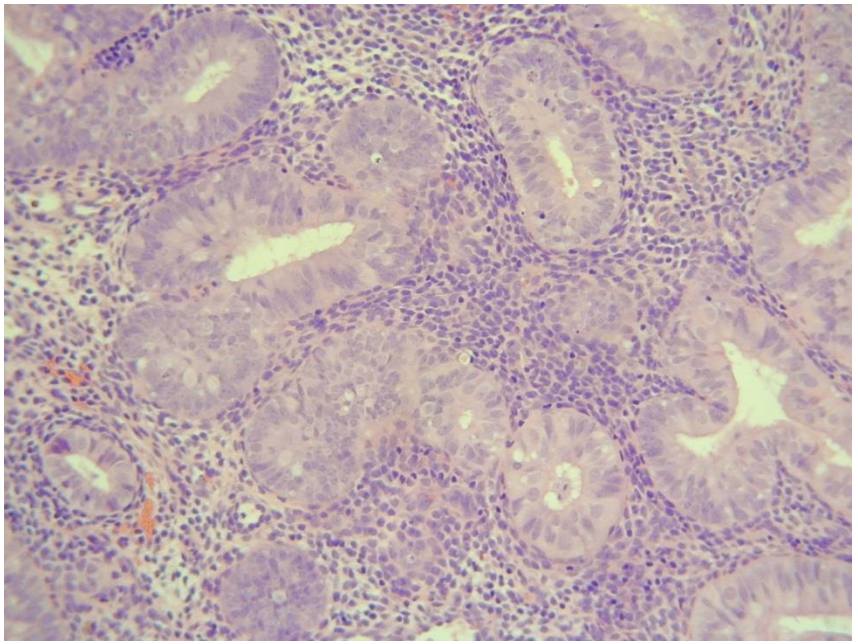
- benign endometria
- hyperplastic endometria (18% morules, 18% tubal, 5% mucinous)
- endometrioid adenocarcinomas

DISTINCTION FROM HYERPLASIA

- often asssociated with hyperplasia
- try to “ignore” metaplasia when assessing whether hyperplasia present and look for architectural changes
- cytology is different to background with metaplasias
- BIG PROBLEM WHEN CROWDED- is it hyperplasia without atypia with metaplastic changes; is it AH; evidence suggests that best regarded as AH

DIFFICULT CASE





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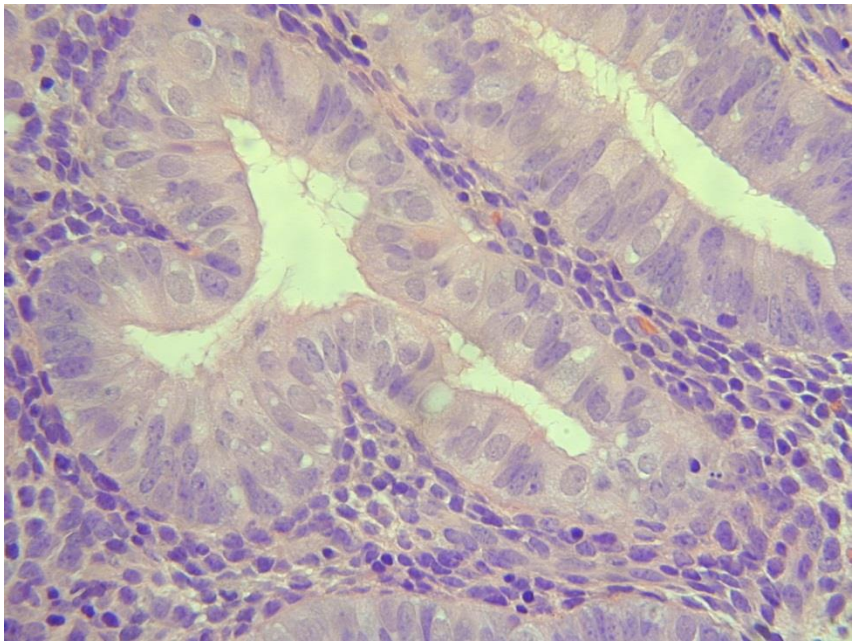

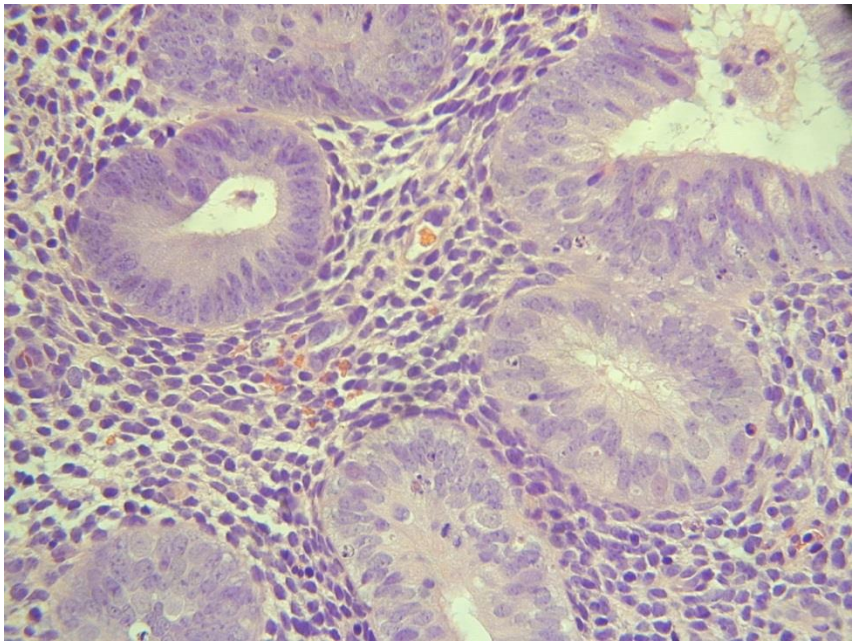

AT PRESENT BETTER TO CONTINUE WITH ATYPICAL HYPERPLASIA CLASSIFICATION (but employ parameters used in EIN diagnosis)

don’t confuse EIN with EIC (endometrial intraepithelial carcinoma - presumed precursor of endometrial serous carcinoma)- serous EIC (terminology in WHO 2014)

EUROPEAN WORKING GROUP CLASSIFICATION

- applies to biopsy specimens only
- practical, managment based scheme
- combines simple and complex hyperplasia into one category (hyperplasia/ hyperplasia without atypia)
- combines atypical hyperplasia and grade 1 endometrioid adenocarcinoma- ENDOMETRIOID NEOPLASIA
- not in widespread use

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Reproducibility of current classifications of endometrial endometrioid glandular proliferations: further evidence supporting a simplified classification

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(2013) *Histopathol*

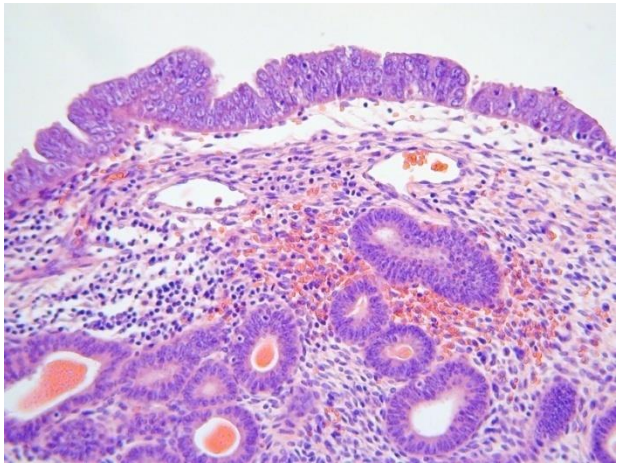
STUDY IN HISTOPATHOLOGY 2014;64;284-292

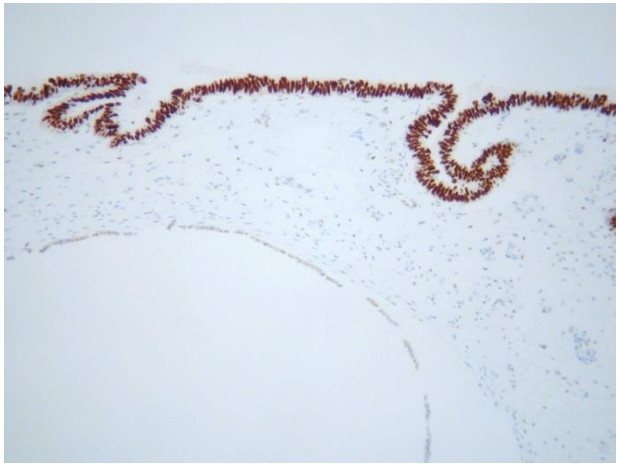
- 9 “expert” observers (Europe and North America)
- 198 biopsies- comparing 3 methods, WHO, EIN, EWG
- WHO, EIN- poor kappas; EWG- moderate kappas
- supports 2 tier classification

POSSIBLE PRECURSORS OF UTERINE SEROUS CARCINOMA

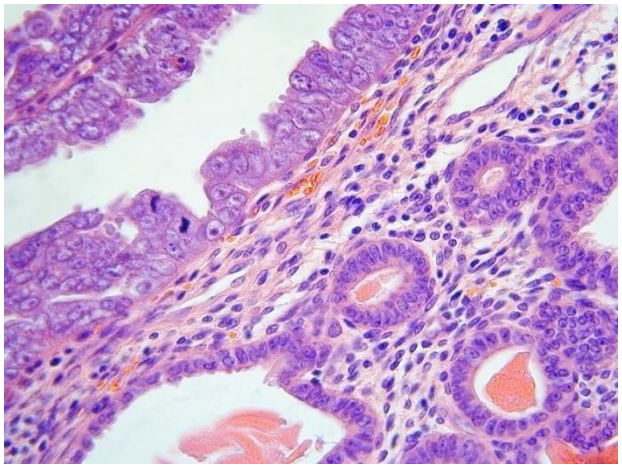
- serous endometrial intraepithelial carcinoma (serous EIC)
- poor term since may result in metastasis
- considered dropping from WHO 2014 but retained
- parallels with STIC

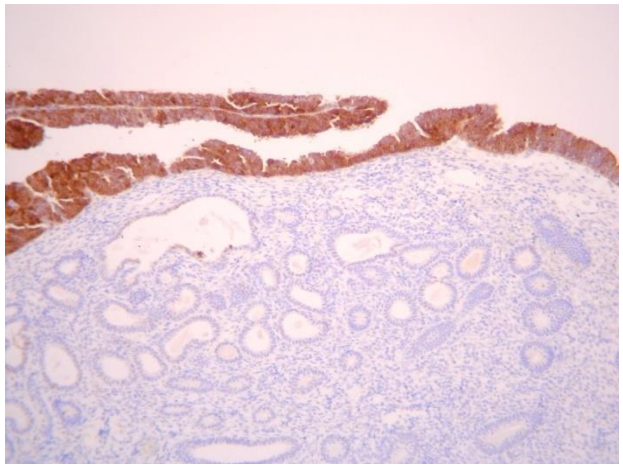
SEROUS EIC (in polyp)





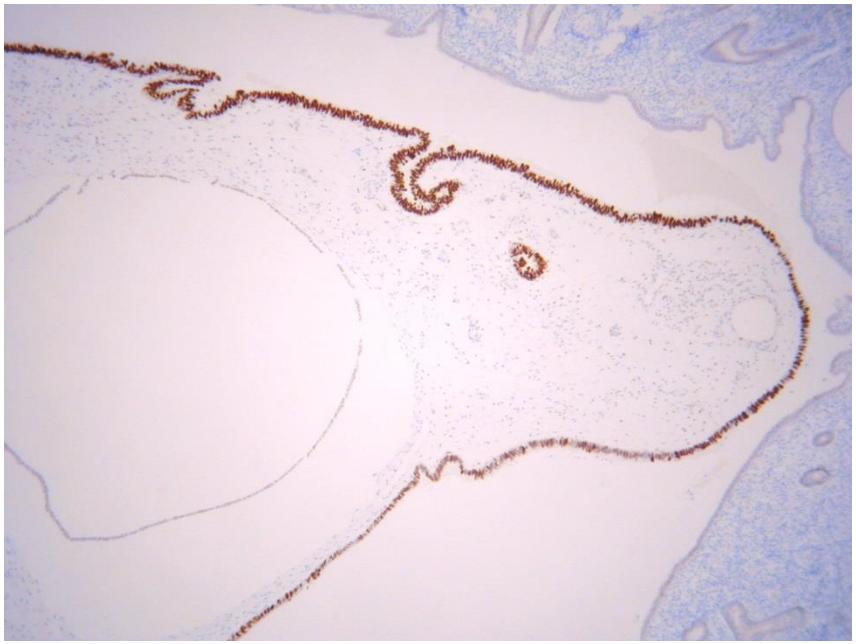
p53





p16

SEROUS EIC (in polyp)



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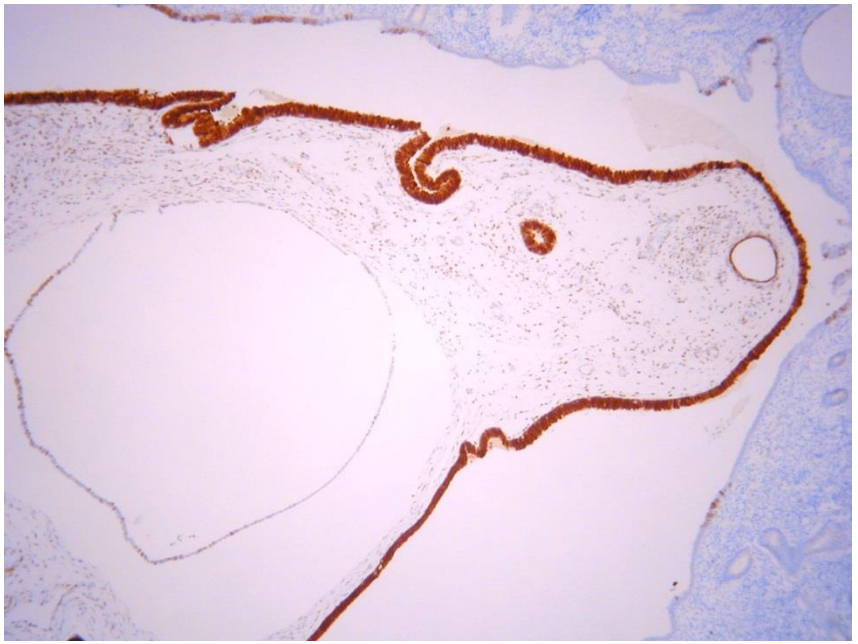

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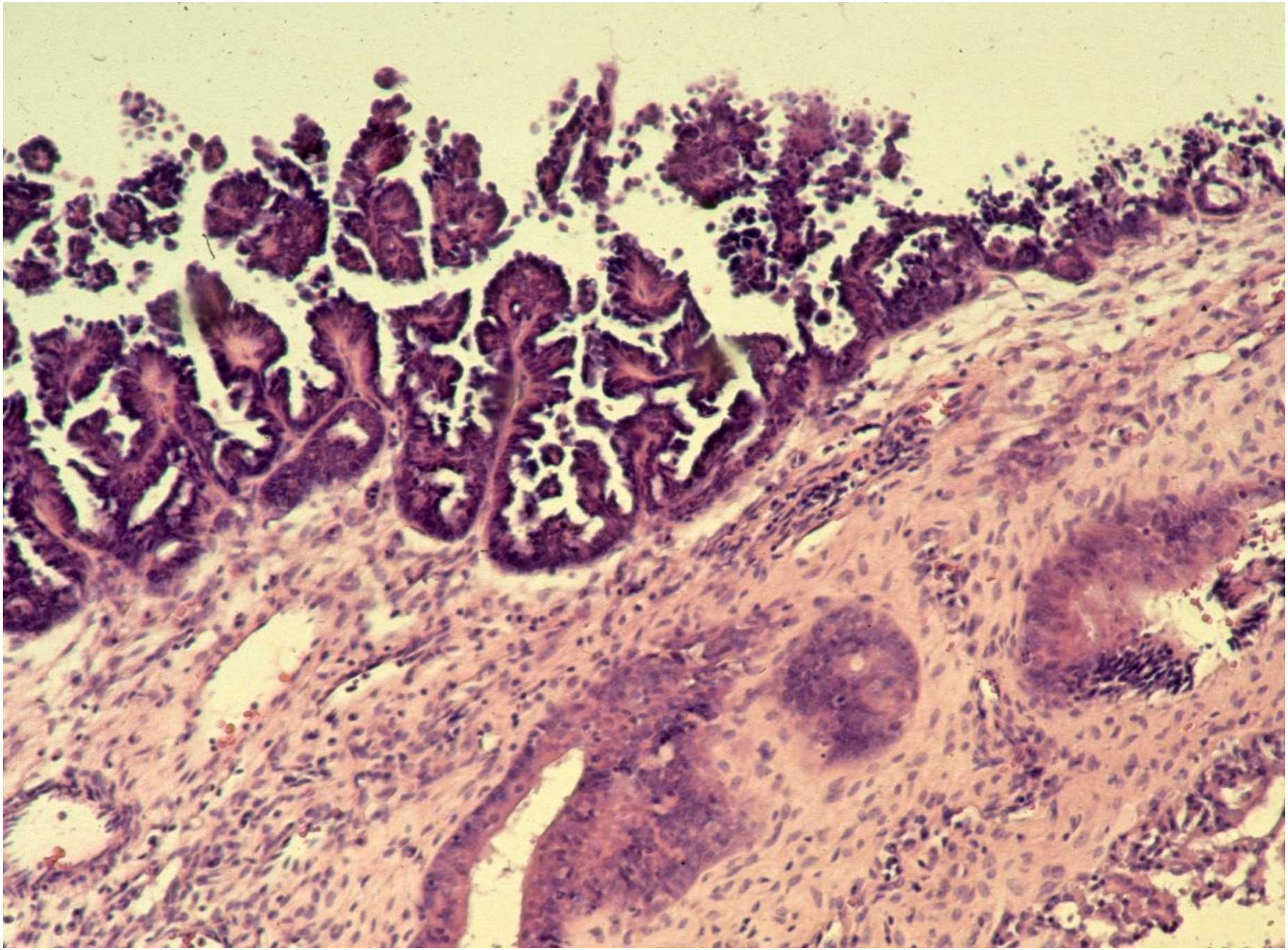
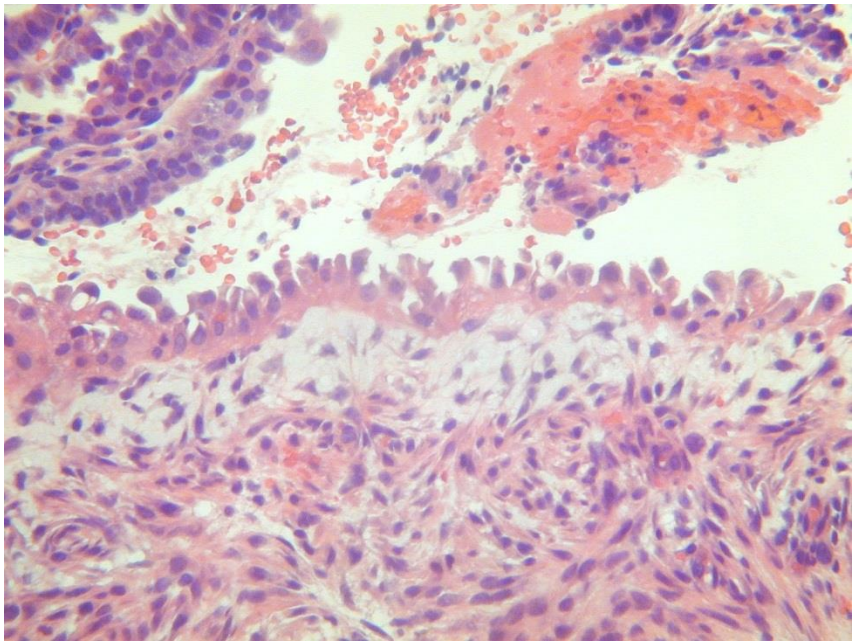
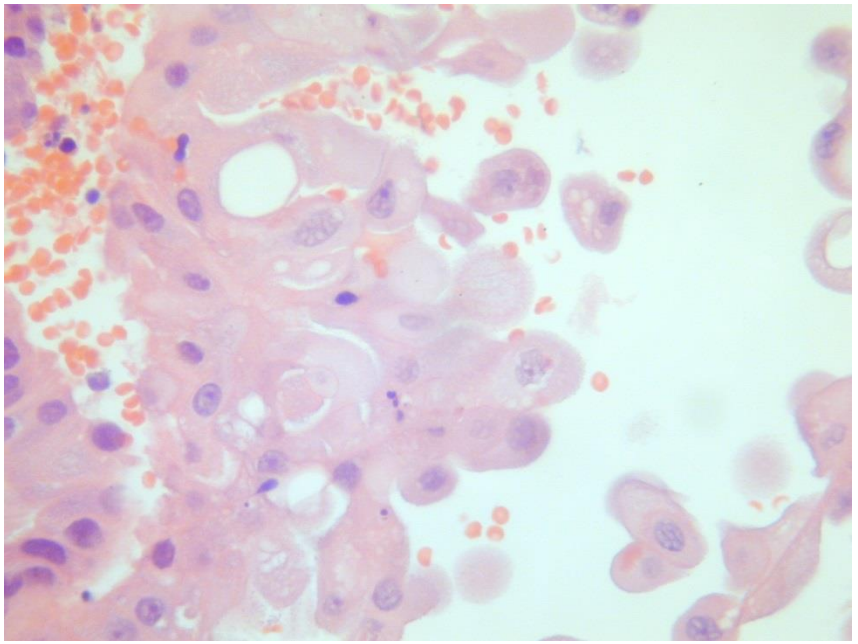


SEROUS EIC- p53

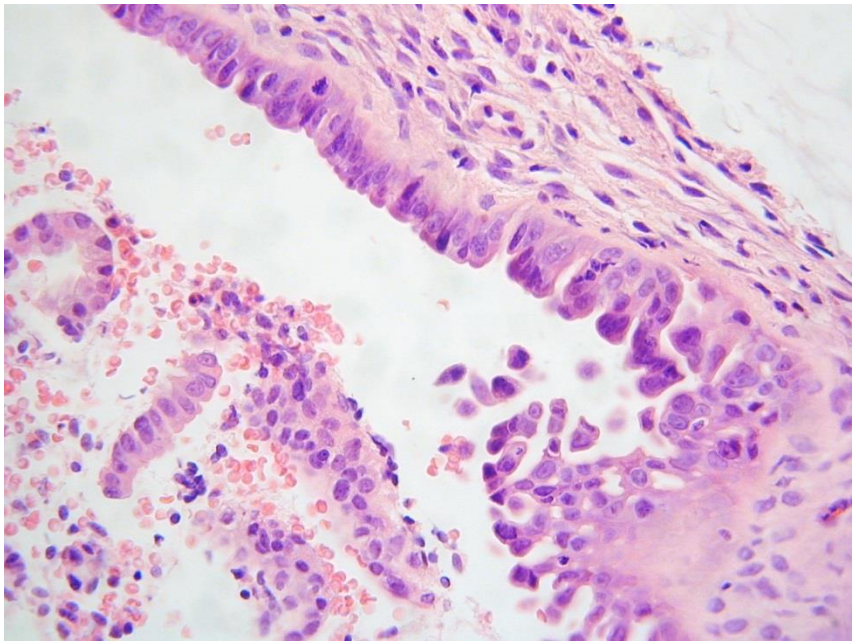
- p53 mutant by definition (“all or nothing”)
- useful in diagnosis and excluding mimics
- “reactive changes” (hobnail on polyp, breakdown, IUD-effect) –p53 often upregulated but “wild-type”

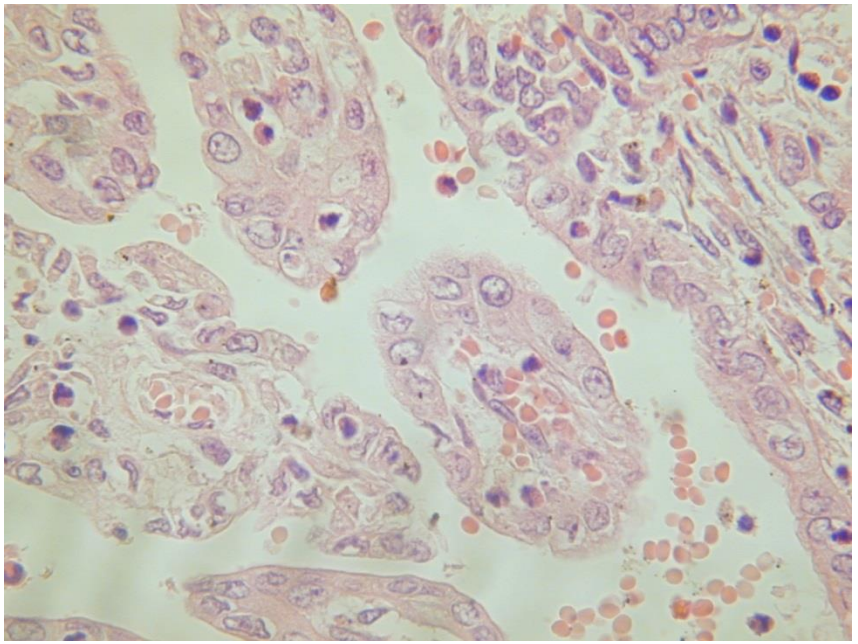
HOBNAIL METAPLASIA ON POLYP





IUD EFFECT





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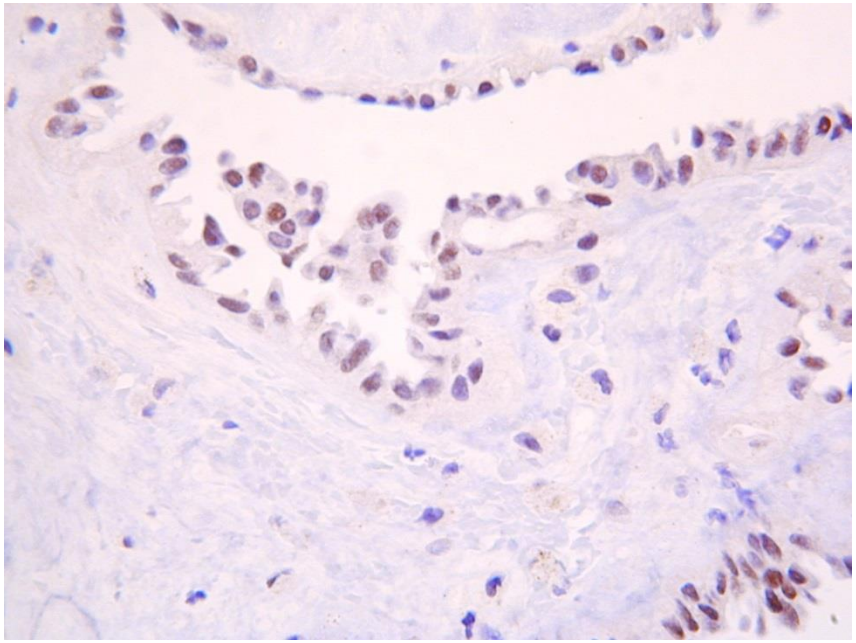
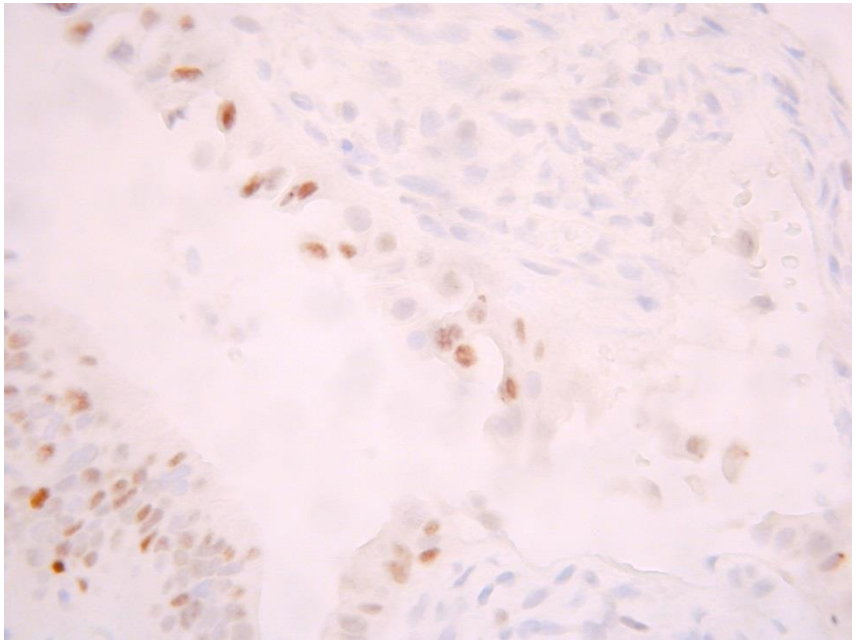


HOBNAIL ATYPIA



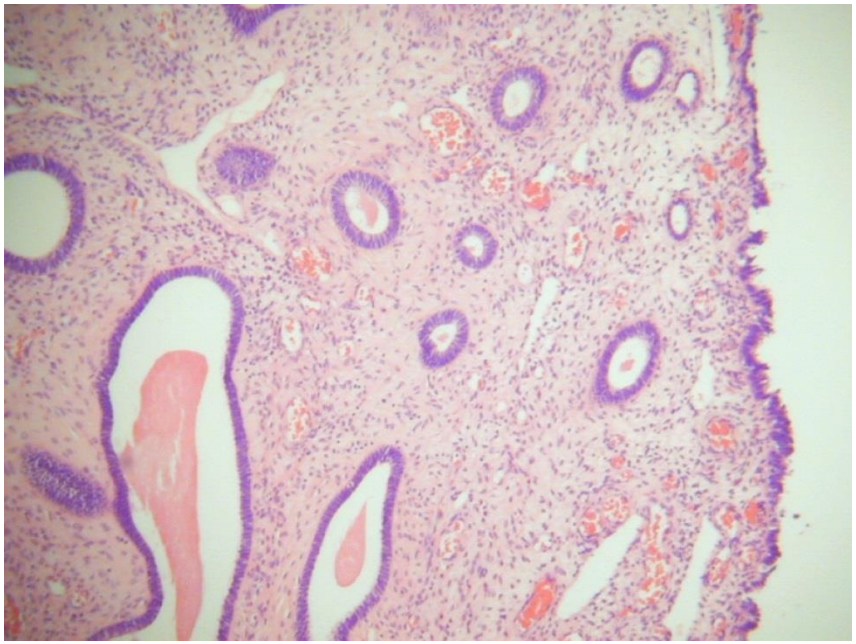
IUD EFFECT

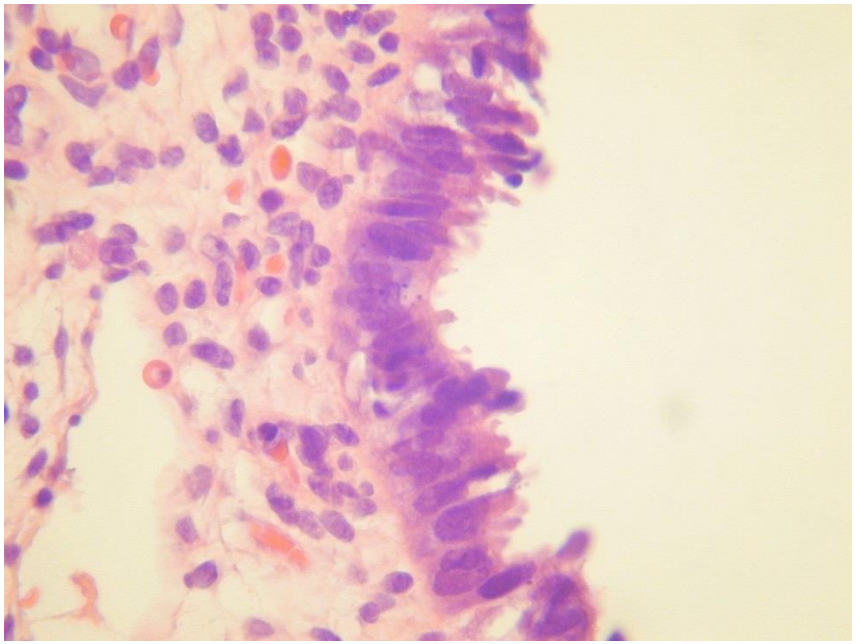
CONCEPT OF ENDOMETRIAL GLANDULAR DYSPLASIA

- postulated precursor of serous EIC
- lesser degrees of cytological atypia
- found in polyps
- found adjacent to serous EIC or USC
- intermediate MIB1
- p53 mutations have been demonstrated (small numbers)
- claimed to have been identified in biopsies taken some time before development of USC

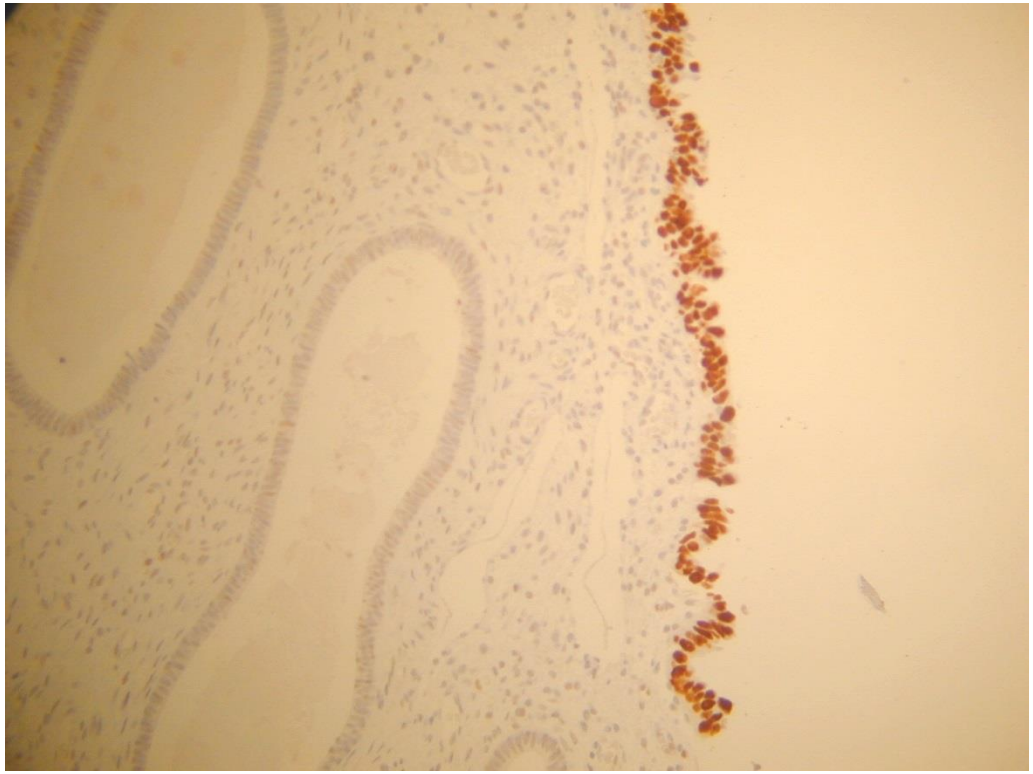
BUT ? JUST MORE SUBTLE SEROUS EIC

EGD





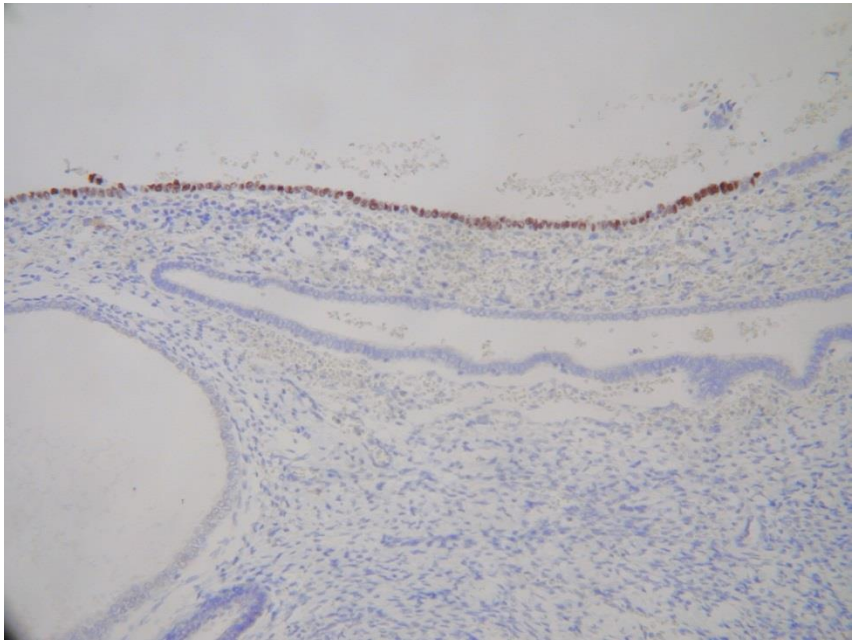
EGD- p53

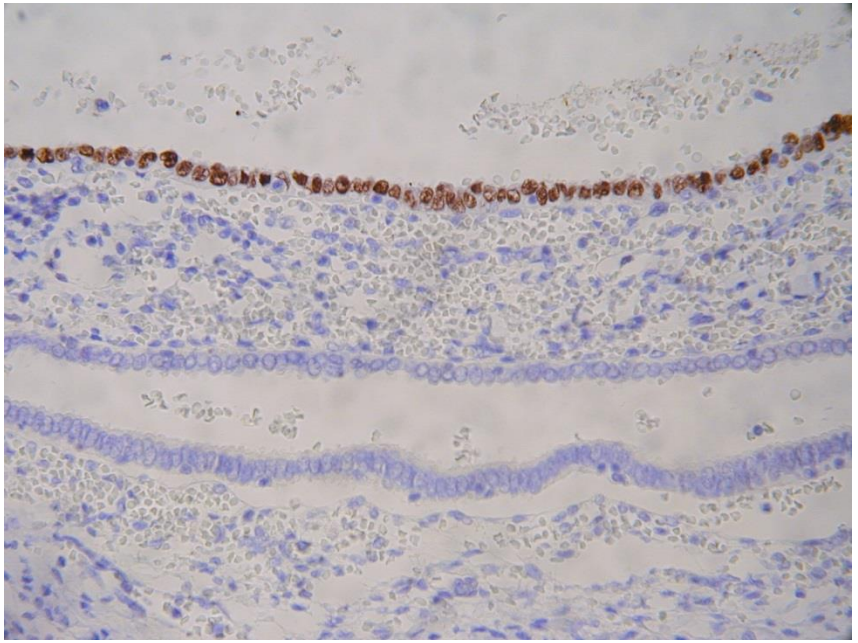


p53 SIGNATURE IN ENDOMETRIUM

- Modern Pathology 2009;22;345-350
- especially in endometrial polyps
- identified in 7 of 10 cases of serous EIC (2 were mutifocal)
- identified in 4% of benign endometrial polyps
- same or different p53 mutations as serous ca in same specimen (small numbers)
- significance unknown but could be earliest stage of endometrial serous neoplasia

p53 SIGNATURE IN ENDOMETRIUM





POSSIBLE MODEL OF ENDOMETRIAL SEROUS CARCINOGENESIS

- p53 mutation (in atrophic endometrium)
- p53 signature
- endometrial glandular dysplasia (first morphological manifestation)
- serous EIC
- serous carcinoma

OBVIOUS PARALLELS WITH TUBAL HIGH GRADE SEROUS CARCINOMA