

Female genital tract-Part2. Pathology of the uterine corpus

Lilla Madaras MD PhD
Department of Pathology, Forensics and Insurance medicine

250 years of EXCELLENCE in medical education, research & innovation and healthcare

24th April 2023

Semmelweis University http://semmelweis.hu

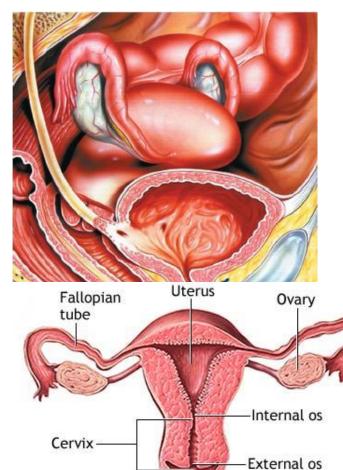


FYI

Those slides with "the blue star" are the most important ones you should focus on when studying for the final exam.

(The others are important too, especially for future gynecologists and pathologists ⊕)

Anatomy, development

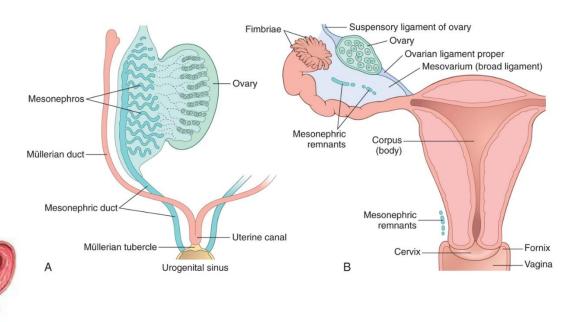


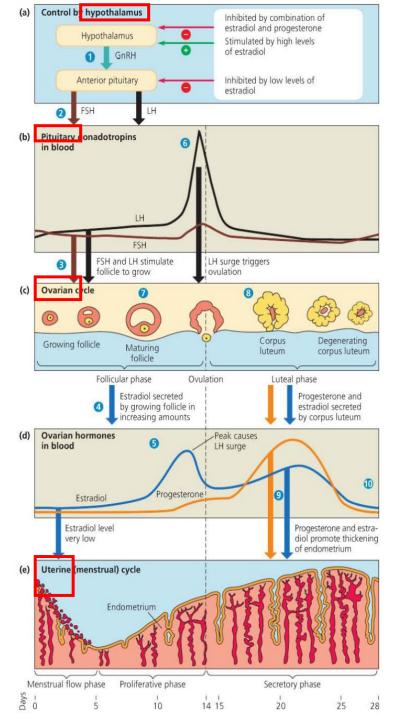
Vagina

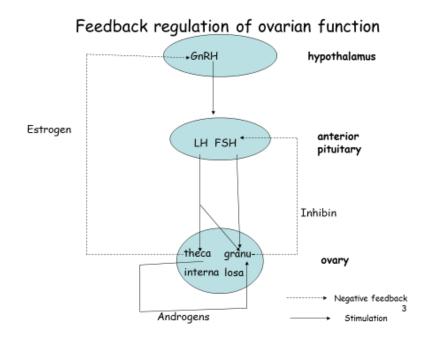
Labium

minus

*ADAM

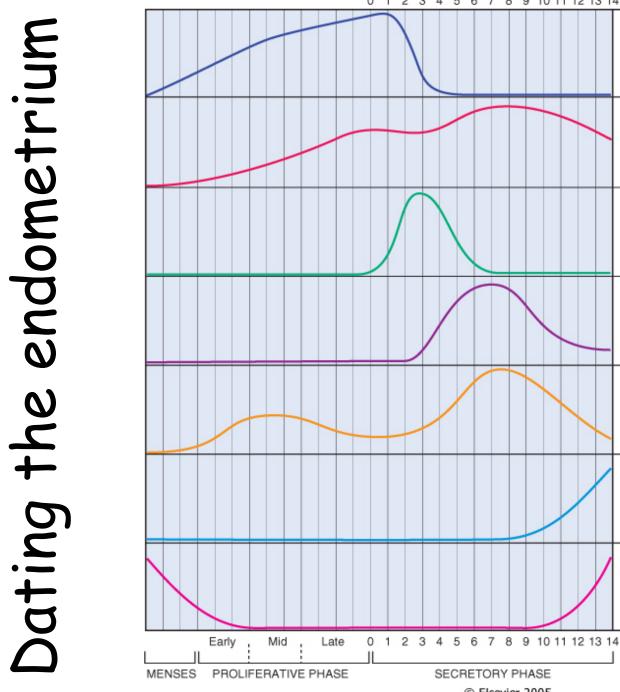






Ovarian and endometrial (menstrual) cycles and their regulation

"Dating" the endometrium



GLAND MITOSES

Gland mitoses indicate proliferation. They occur during menstruation because repair and breakdown are progressing simultaneously.

TORTUOSITY OF GLANDS

Gland development parallels endometrial thickness. It has two phases, the earliest stimulated by estrogen. During secretory phase, tortuosity becomes pronounced, paralleling the secretion curve.

BASAL VACUOLATION

This is the earliest morphologic evidence of ovulation found in the endometrium. It begins approximately 36 to 48 hours after ovulation.

SECRETION

This curve represents visible secretion in the gland lumen. Active secretion falls off more abruptly. In the later stages, the secretion becomes inspissated.

STROMAL EDEMA

Edema varies with the individual, particularly the rise during proliferation, which may be almost absent. The edema that accompanies secretion is more constant.

PREDECIDUAL REACTION

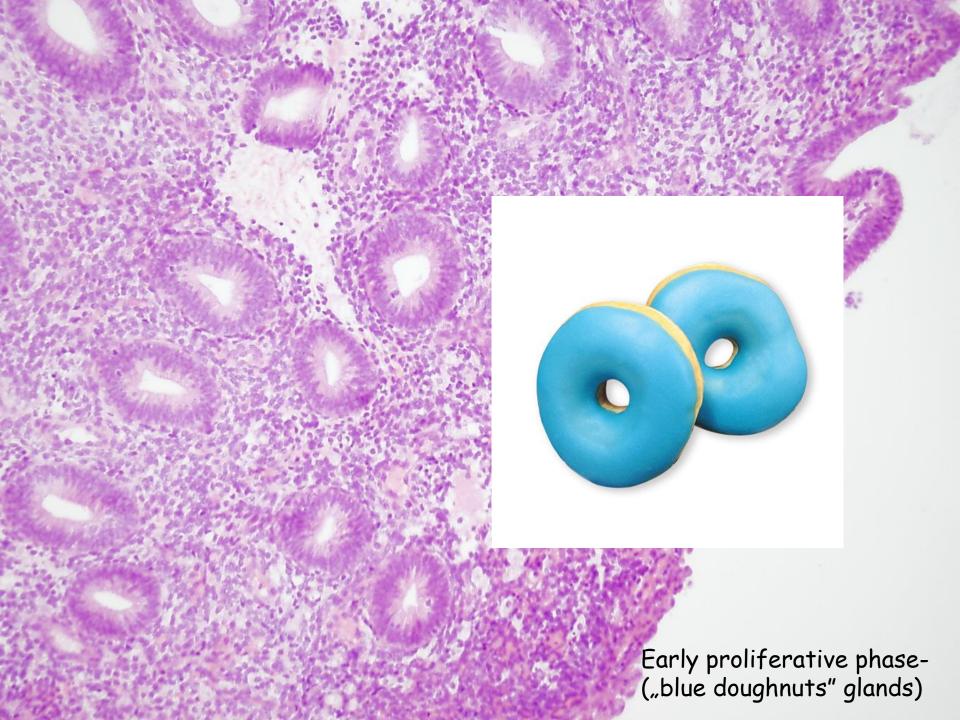
This is evident first around the arterioles and progresses until just before menstruation. A superficial compact layer is formed beginning on day 11 post ovulation.

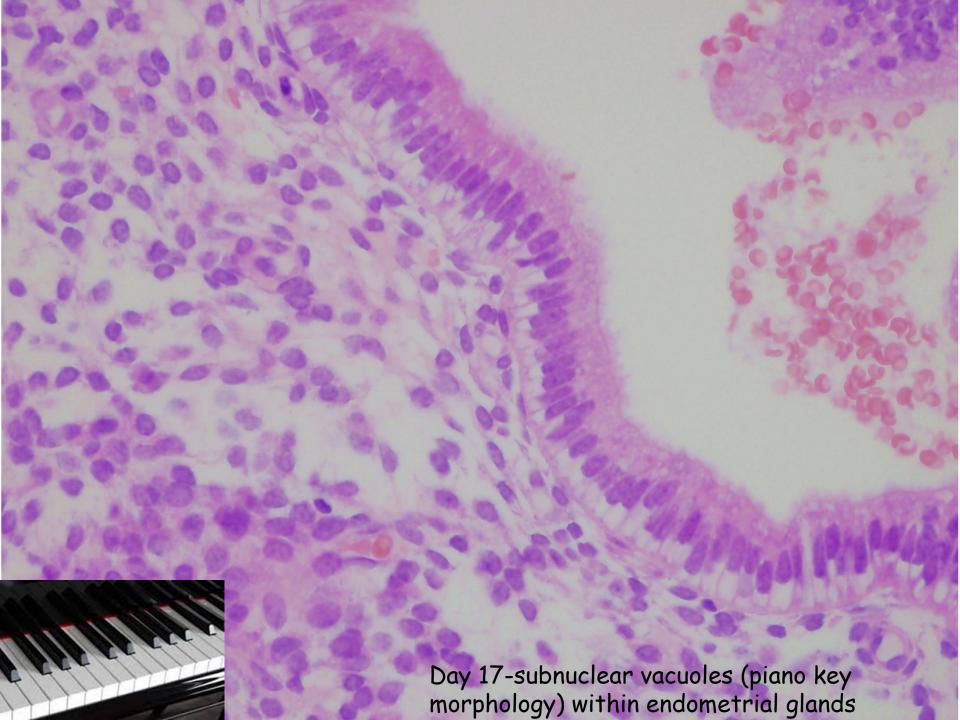
LEUKOCYTIC INFILTRATION

Throughout the cycle, there are always a few lymphocytes. Neutrophil infiltration begins about 2 days before the onset of flow.

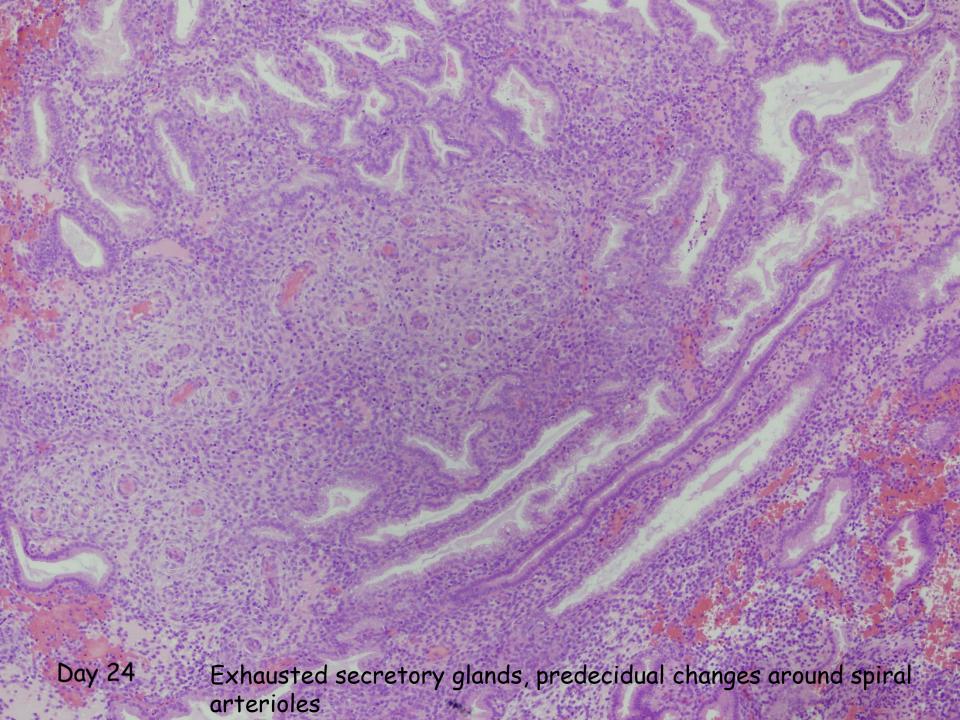
SECRETORY PHASE

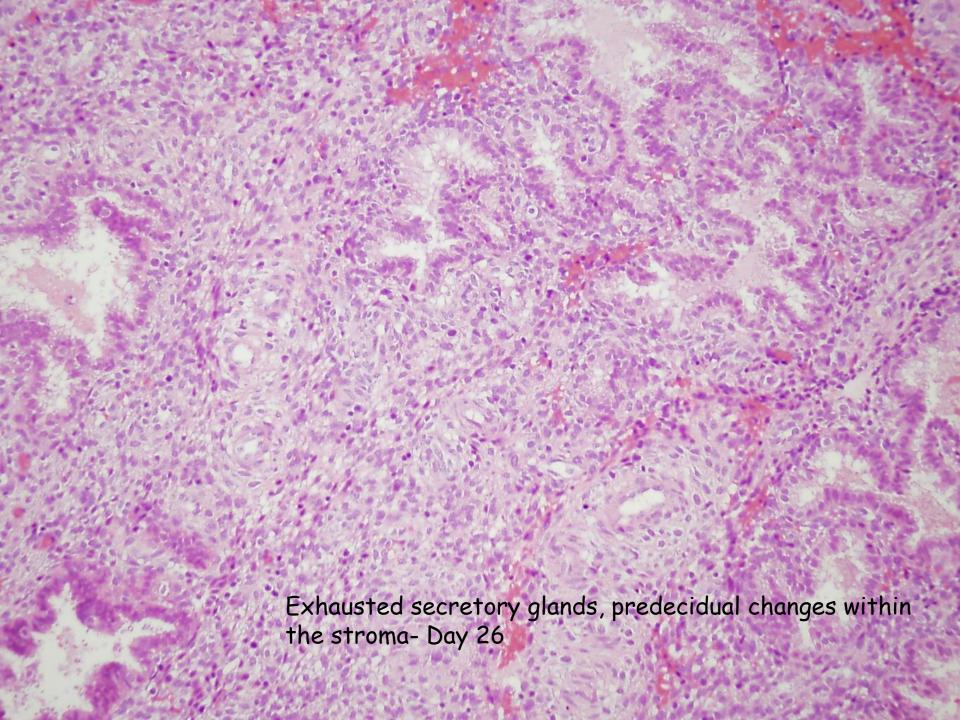
© Elsevier 2005

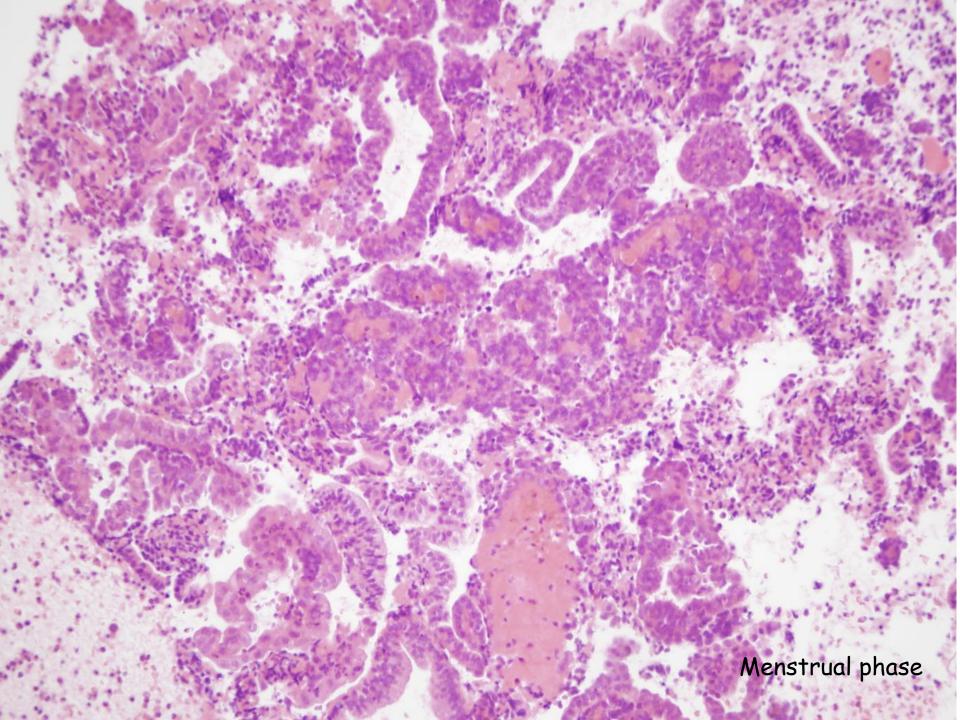


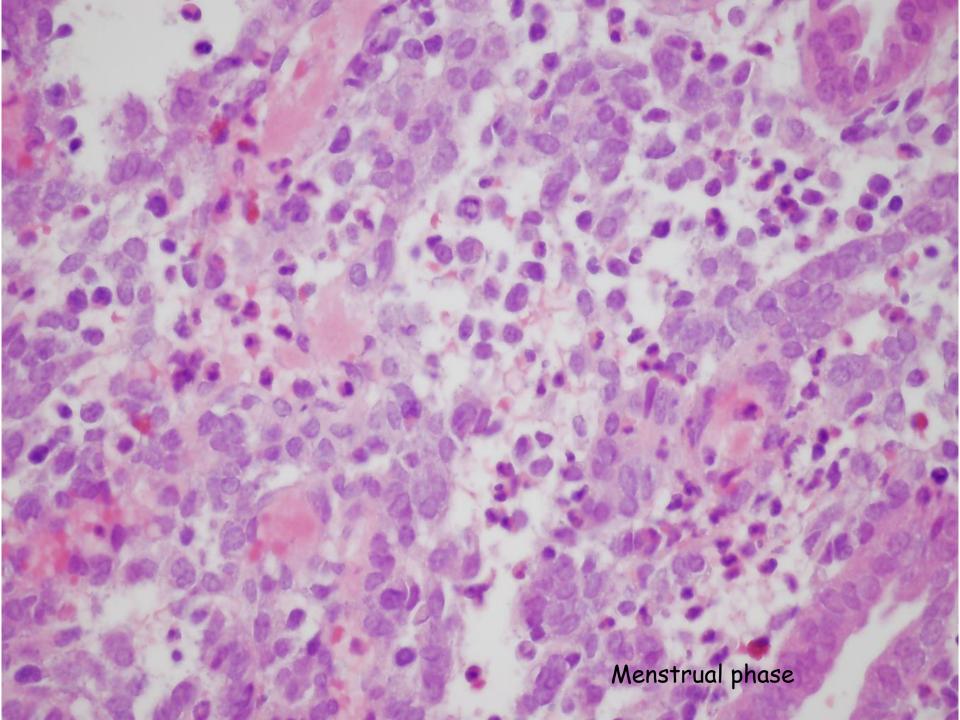












How do we assess the endometrium?

1. By sampling procedures

2. In hysterectomy specimens (from TAH with or without BSO, laparoscopic hysterectomy, Chrobak surgery, Wertheim surgery...)

Endometrium Sampling Techniques

1. Dilatation and Curettage(D&C)

2. Fractional curettage (separate sampling of the endometrium and endocervix)

3. Hysteroscopy+ polyp/endometrium ablation

4. Endometrial biopsy (Pipelle)

Biopsy Catheter

Uterus

Vagina

Cervix

Vagina

www.fmhs.auckland.ac.nz

Endometrial Biopsy

Endometrial sampling-when?

- AUB (abnormal uterine bleeding)
- Abortion
- "Dating" the endometrium in cases of infertility
- Hormone replacement therapy, Tamoxifen

Pathology of the endometrium

- Inflammation
- Clinical terms
- · AUB
- · Endometrial hyperplasia
- · Adenomyosis end endometriosis
- · Tumors of the endometrium



Inflamr

- · Acute endometritis
 - in abortion, in a postpartum sta
 - group A hemolytic streptococci,
- · Chronic endometritis
 - after retained gestational tissu
 - in PID
 - due to an IUD (actinomyces!)
 - tuberculosis (from tubercolous western world
 - chlamydial infection- plasma cel
- Pyometra
- Asherman's syndrome (intrainesulting in amenorrhea)



fan twees

Clinical terms (still in your book and in use)

- · amenorrhea- primary or secondary
- · hypomenorrhea

 menorrhagia
- · metrorrhagia
- · dysmenorrhea



Clinical terms

- Dysfunctional uterine bleeding
- · Oligomenorrhea, polymenorrhea
- · hypomenorrhea menorrhagia
- Metrorrhagia, metropathia haemorrhagica
- · Dysmenorrhea



SPECIAL COMMUNICATIO

FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age

Malcolm G. Munro a.b.*, Hilary O.D. Critchley c, Michael S. Broder d, Ian S. Fraser c; for the FIGO Working Group on Menstrual Disorders

- * Department of Obstetrics and Gynecology, University of California, Los Angeles, USA
 * Kaiser Permanente, Los Angeles Medical Center, Los Angeles, USA
- Centre for Reproductive Biology, University of Edinburgh, Queen's Medical Research Institute, Edinburgh, UK
 Partnership for Health Analytic Research, Beverly Hills, USA
- * University of Sudney Owen Flizabeth II Research Institute for Mathers and Infants Sudney
- Abnormal Uterine Bleeding (AUB)

AUB facts

- Premenop AUB- 1/3 of gynecological consultations
- Peri- and postmenop AUB- 70% of gynecological consultations
- FIGO Menstrual Disorders Working Group-2011
- American College of Obstetricians and Gynecologists (ACOG)-2013

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* Brotznershin for Hodelh Analytic Besearch, Research Bills USA

^{*} Department of Obstetrics and Gynecology, University of California, Los Angeles, USA

AUB definitions

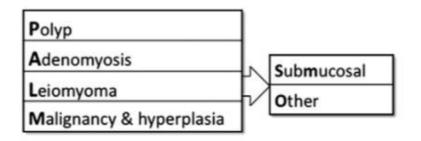
 AUB: bleeding from the uterine corpus that is abnormal in volume, regularity, and/or timing

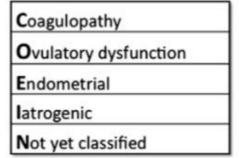
- Heavy menstrual bleeding (HMB)
- Intermenstrual bleeding (IMB)

AUB definitions (cont.)

- Chronic AUB: bleeding from the uterine corpus that is abnormal in volume, regularity, and/or timing, and has been present for 6 months
- Acute AUB: was defined as an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent further blood loss
- · Intermenstrual bleeding (IMB): occurs between clearly defined cyclic and predictable menses

AUB in reproductive ages PALM/COEIN









PALM

- · Polyp-AUB-P
- · Adenomyosis AUB-A
- · Leiomyoma AUB-L
- · Malignancy and hyperplasia AUB-M

 These lesions are detected by imaging and assessed by histology

Causes of Abnormal Uterine Bleeding by Age Group

Prepuberty	Precocious puberty (hypothalamic, pituitary or ovarian origin)	
Adolescence	Anovulatory cycle	
Reproductive age	Complication of pregnancy (abortion, trophobl.disease, ectopic pregnancy)	
	Organic lesions (leiomyoma, polyp, adenomyosis, endometrial hyperplasia, carcinoma)	
	Anovulatory cycle	
Perimenopausal	Anovulatory cycle	
	Organic lesions (carcinoma, hyperplasia, polyp)	
Postmenopausal	Organic lesions (carcinoma, hyperplasia, polyp) Endometrial atrophy	27

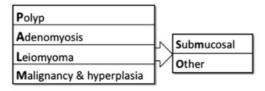
Dysfunctional endometrial bleeding (now AUB-COEIN group)

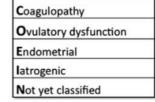
Inadequate proliferative phase

 discrepancy between the observed and the expected endometrial pattern in the proliferative phase

· Inadequate luteal phase

- low progesteron level
- infertility
- amenorrhea or abnormal bleeding
- sampling 2 days before expected menstruation!
- Irregular shedding of the endometrium
 - menstruation lasts longer than 7 days without prolongation of the cycle
 - sampling on the 5th day of the menstruation demonstrates menstruation type and late secretory type endometrium and early proliferative endometrium









Dysfunctional endometrial bleeding

Anovulatory cycle (AUB-O)

- in adolescence and premenopausa most commonly due to slight hormonal imbalances and no apparent causes

- Less commonly:

- endocrine causes: thyroid, adrenal or pituitary disease
- · ovarian causes: PCO, granulosa-theca cell tumor
- systemic metabolic causes: obesity, malnutrition (anorexia nervosa!), chronic systemic diseases etc.
- no ovulation→ prolonged unopposed estrogenic stimulation → persistant proliferative endometrium → endometrial hyperplasia or unsheduled breakdown of the stroma → abnormal bleeding



Endometrial hyperplasia

 result of unopposed, prolonged estrogenic stimulation (due to anovulation or increased estrogen production-PCO, Stein-Leventhal sy, cortical stromal hppl, estrogen replacement therapy, functioning granulosa cell tumor)

- · (Simple or Complex) Hyperplasia without
- · (Simple or Complex) Hyperplasia with atypia

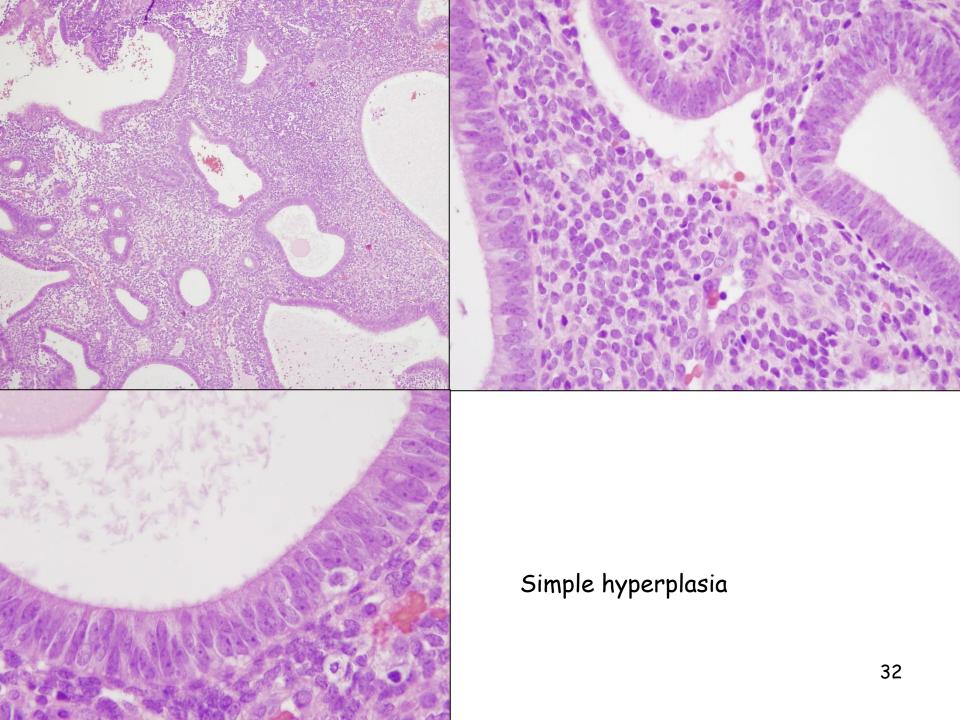
Hyperplasia (formerly called simple hyperplasia)

· Without atypia

- diffuse alteration
- increased amount of glands and stroma
- (Mildly increased) almost normal ratio of glands and stroma
- differences in glandular size and shape
- cystically dilated glands
- glandular epithelium: proliferative
- Usually no progression to adenocarcinoma (1%)

· With atypia

- the previous features + cytological atypia
- Uncommon
- Progression to adenocarcinoma 8%

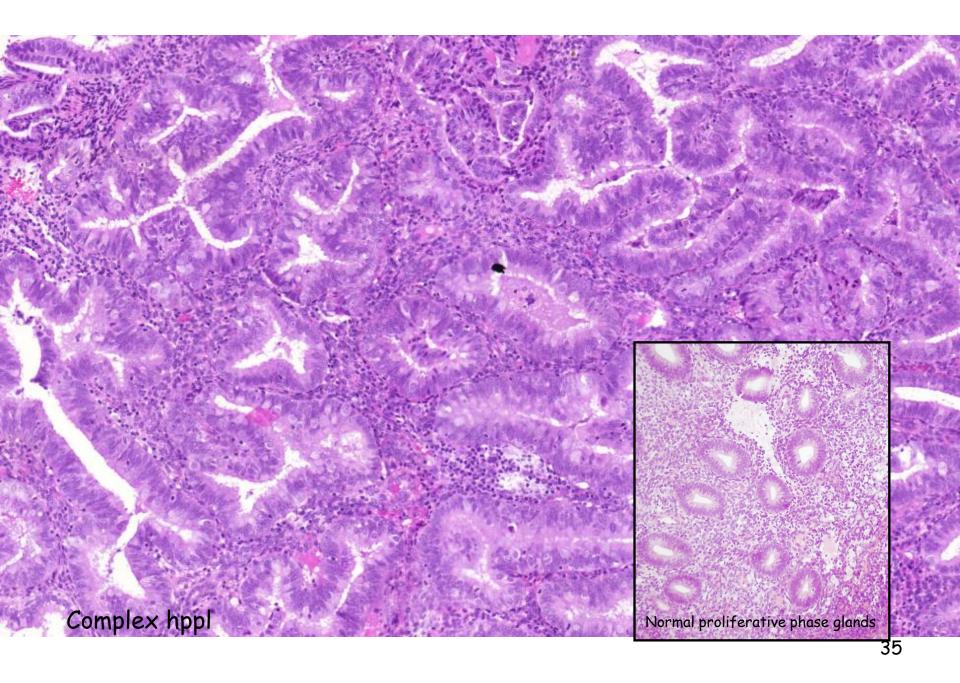




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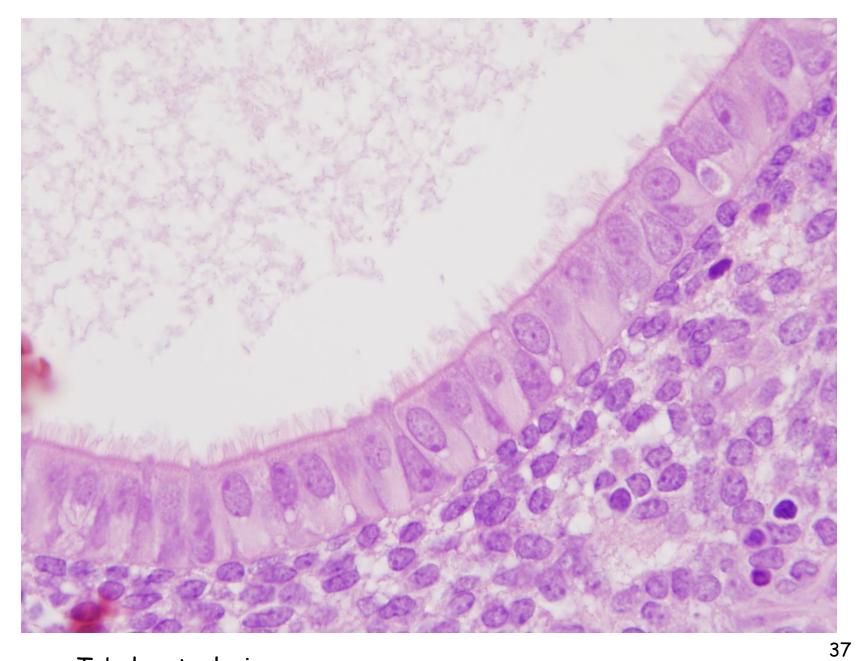
Formerly called complex hyperplasia

- Without atypia
 - focal alteration
 - irregular glands
 - increased ratio of glands to stroma (less intervening stroma, back-to-back placed glands)
 - Progression to adenocarcinoma 3%
- With atypia (Endometrioid Intraepithelial Neoplasia)
 - cytological atypia
 - Usually hysterectomy is done
 - Progression to adenocarcinoma 25-30%



Metaplasias

- different forms: squamous, tubal, eosinophilic, mucinous, etc.
- · frequently associated with hyperplasia



Tubal metaplasia

Adenomyosis and endometriosis

- Adenomyosis: endometrial glands and stroma deep within the myometrium (by at least 2-3 mm from endometrium)
- Endometriosis: endometrial tissue outside the uterus
 - made of functional endometrium undergoing cyclic changes
 - origin from müllerian rests?
 implantation?lymphatic or hematogenous spread?
 - most commonly within the ovaries, uterine ligaments, on the pelvic peritoneum, bowel, appendix, cervix, fallopian tube, laparotomy scars
 - pelvic pain, dysmenorrhea, infertility

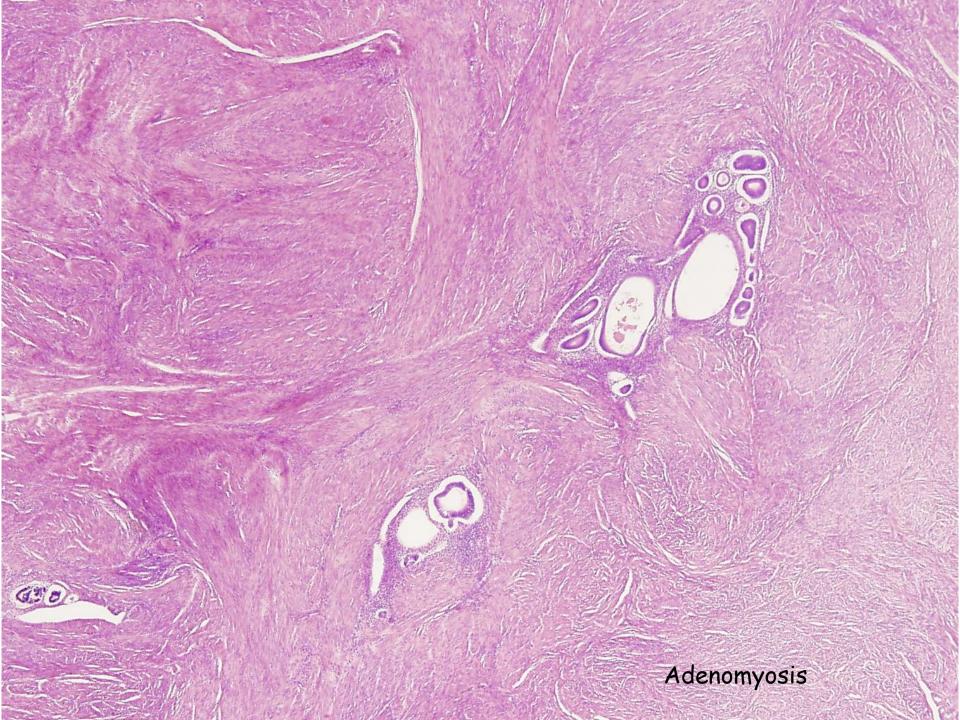
- Deep infiltrating endometrosis (DIE)





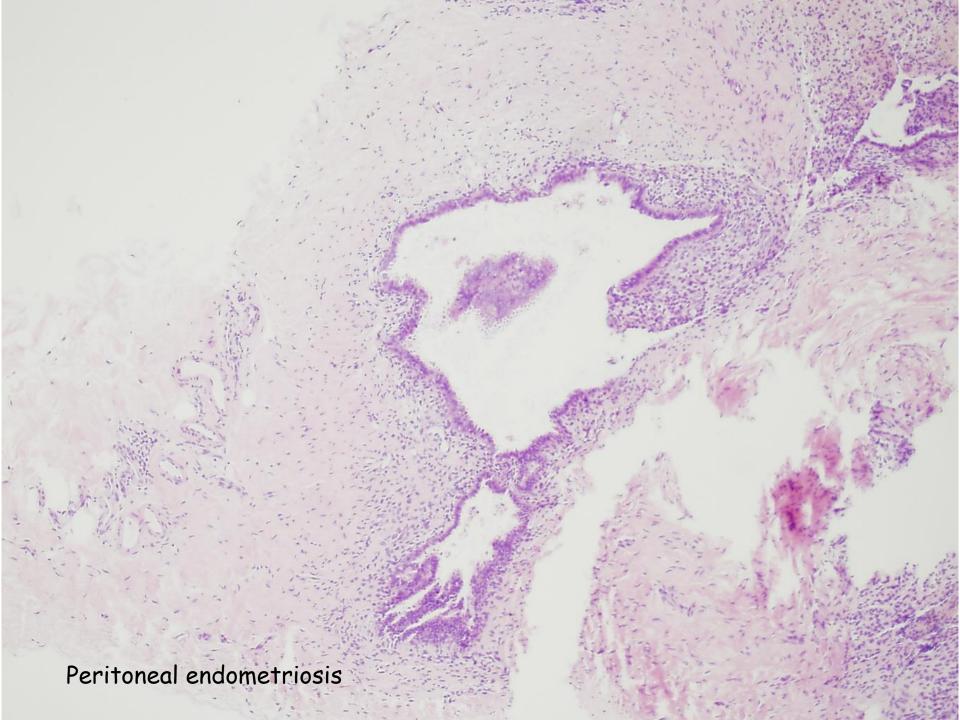
Adenomyosis

5081





Endometriosis of ovary- cyst formation (chocolate cyst)

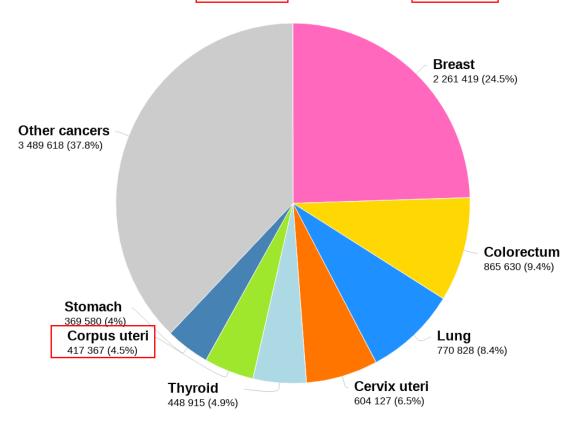


Endometrial polyps

- · not true neoplasms, exophytic mass
- may occur after Tamoxifen (SERM) administration
- asymptomatic or may produce abnormal bleeding (AUB-P)
- · MA: projects into the body cavity
- MI: cystically dilated glands, fibrous stroma and thick-walled vessels
- adenocarcinoma arising in ~ is possible

UTERINE NEOPLASIAS

Estimated number of new cases in 2020, World, females, all ages



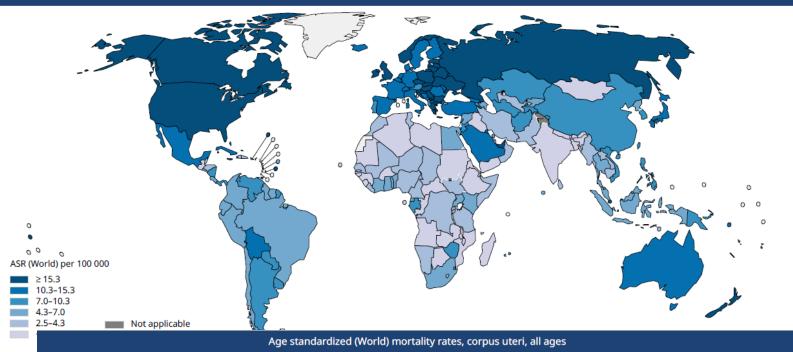
Total: 9 227 484

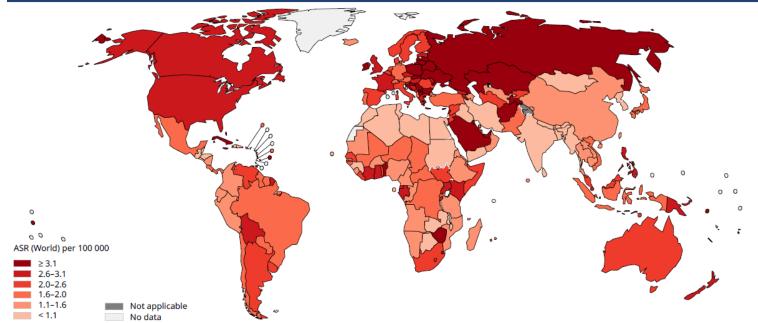


Tumors of the uterine corpus

Arising from		Benign	Malignant
Endometrium	Endometrial glands	-	Endometrioid carcinoma Serous cc Clear cell cc
	Endometrial stroma	Stromal nodule	Stromal sarcoma
	Endometrial glands and stroma	Adenofibroma Adenomyoma	Carcinosarcoma Adenosarcoma
Myometrium		Leiomyoma	Leiomyosarcoma

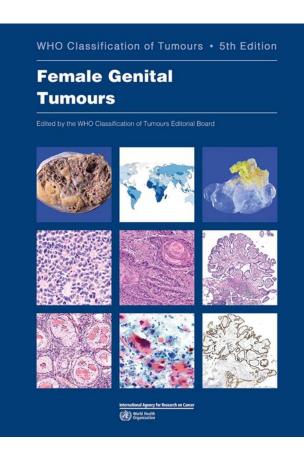
Age standardized (World) incidence rates, corpus uteri, all ages





Data source: GLOBOCAN 2018

Graph production: IARC (http://gco.iarc.fr/today)



Endome	trial epithelial tumours and precursors	8897/1	Smooth muscle tumour of uncertain malignant poten
	Endometrial hyperplasia without atypia	8891/1*	Epithelioid smooth muscle tumour of uncertain malignant potential
8380/2	Atypical hyperplasia of the endometrium	8896/1*	Myxoid smooth muscle tumour of uncertain
8380/3	Endometrioid adenocarcinoma NOS POLE-ultramutated endometrioid carcinoma	0030/1	malignant potential
	Mismatch repair—deficient endometrioid carcinoma		Spindle smooth muscle tumour of uncertain
	p53-mutant endometrioid carcinoma		malignant potential
	No specific molecular profile (NSMP) endometrioid	8898/1	Metastasizing leiomyoma
	carcinoma	8890/3	Leiomyosarcoma NOS
8441/3	Serous carcinoma NOS		Spindle leiomyosarcoma
8310/3	Clear cell adenocarcinoma NOS	8891/3	Epithelioid leiomyosarcoma
8020/3	Carcinoma, undifferentiated, NOS	8896/3	Myxoid leiomyosarcoma
8323/3	Mixed cell adenocarcinoma	8930/0	Endometrial stromal nodule
9110/3	Mesonephric adenocarcinoma	8931/3	Endometrial stromal sarcoma, low grade
8070/3	Squamous cell carcinoma NOS	8930/3	Endometrial stromal sarcoma, high grade
8144/3	Mucinous carcinoma, intestinal type	8805/3	Undifferentiated sarcoma
9111/3*	Mesonephric-like adenocarcinoma	8590/1	Uterine tumour resembling ovarian sex cord tumour
8980/3	Carcinosarcoma NOS	8714/0	Perivascular epithelioid tumour, benign
		8714/3	Perivascular epithelioid tumour, malignant
Tumour-	like lesions	8825/1	Inflammatory myofibroblastic tumour
	Endometrial polyp		Epithelioid myofibroblastic sarcoma
	Endometrial metaplasia	Miyada	pithelial and mesenchymal tumours
	Arias-Stella reaction	8932/0	Adenomyoma NOS
Masana	hymal tumours specific to the uterus	8932/0	Atypical polypoid adenomyoma
8890/0	Leiomyoma NOS	8933/3	Adenosarcoma
8890/0	Lipoleiomyoma	Gadaya	, 135715531155715
8890/0	Leiomyoma, apoplectic	Miscella	neous tumours
8890/0	Leiomyoma, hydropic	9473/3	Primitive neuroectodermal tumour NOS
8890/0	Dissecting leiomyoma	9064/3	Germ cell tumour NOS
8892/0	Cellular leiomyoma	9071/3	Yolk sac tumour NOS
8896/0	Myxoid leiomyoma	9080/0	Mature teratoma NOS
8891/0	Epithelioid leiomyoma	9080/3	Immature teratoma NOS
8893/0	Symplastic leiomyoma		
8890/1	Leiomyomatosis NOS		
8890/1	Intravenous leiomyomatosis		



Endometrial carcinoma

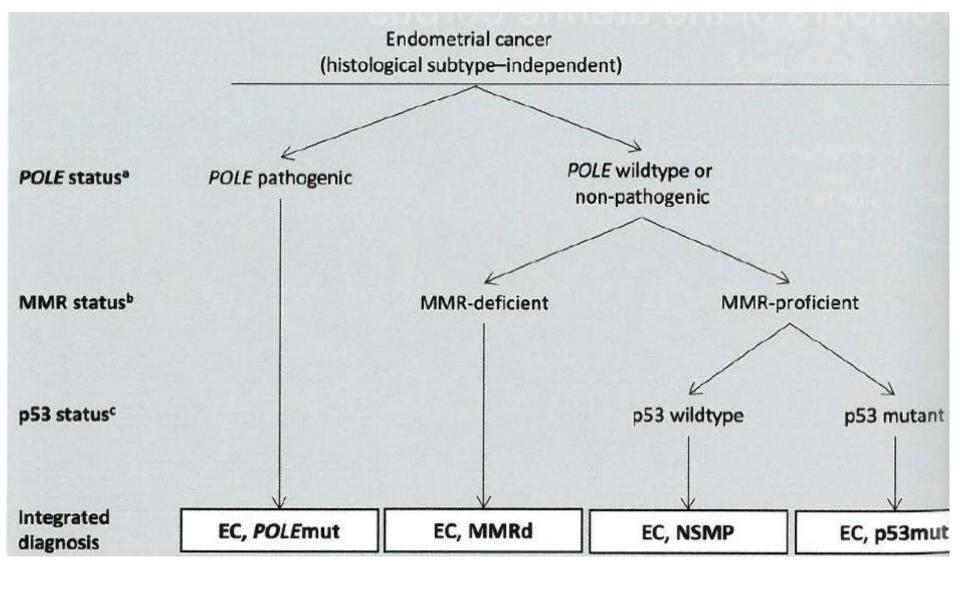
- · 7% of all (non-skin) cancers in women
- · The most common gynecological cancer
- mainly in postmenopausal woman (55-65 y)
- · Sentinel cancer in Lynch syndrome
- · SY: usually postmenopausal bleeding

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8893/0	Symplastic leiomyoma		
8890/1	Leiomyomatosis NOS		

Intravenous leiomyomatosis

8890/1

WHO, 5th edition, 2020



WHO 5th edition, 2020 (ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer)

POLEmut: hotspot mutations of DNA polymerase epsilon (POLE)

MMR: mismatch repair

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Endometrial carcinoma

Endometrioid carcinoma

- on a background of endometrial hyperplasia
- Obesity, diabetes, hypertension, infertility, Stein-Leventhal sy, longstanding estrogen users, breast cancer patients treated with Tamoxifen
- more favorable prognosis
- usually well differentiated

Endometrial carcinoma

- · Endometrioid carcinoma (cont)
 - Grading
 - Grade 1: if<5% solid growth,
 - Grade 2:if < 50% solid growth
 - Grade 3: if > 50% solid growth

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Intravenous leiomyomatosis

8890/1

WHO, 5th edition, 2020



Endometrial carcinoma

- Serous carcinoma

- not associated with endometrial hyperplasia
- Usually in the setting of atrophy
- Poorly differentiated, aggressive
- high grade cytologic features, necrosis, lymphovascular invasion, transtubal spread
- Papillary, glandular
- mutation of TP53
- Early lesion: Serous Endometrial Intraepithelial Carcinoma (SEIC)

Endometrial carcinoma

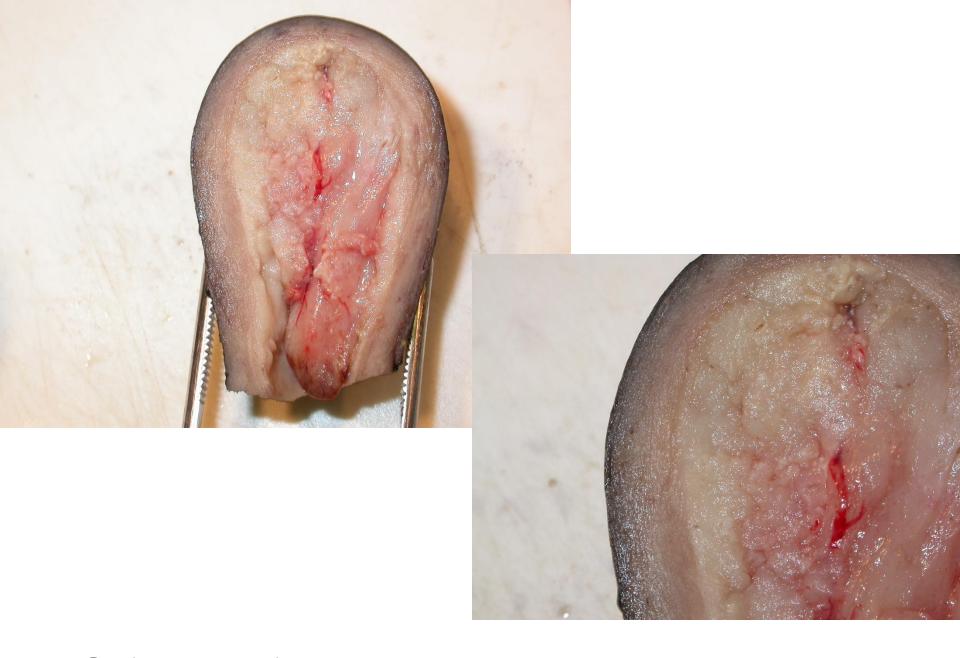
Spread and metastases



- local spread: myometrium and cervix
- extrauterine spread: pelvic and paraaortic lymph nodes, ovaries
- serous carcinoma: early spread to the peritoneum, transtubal spread

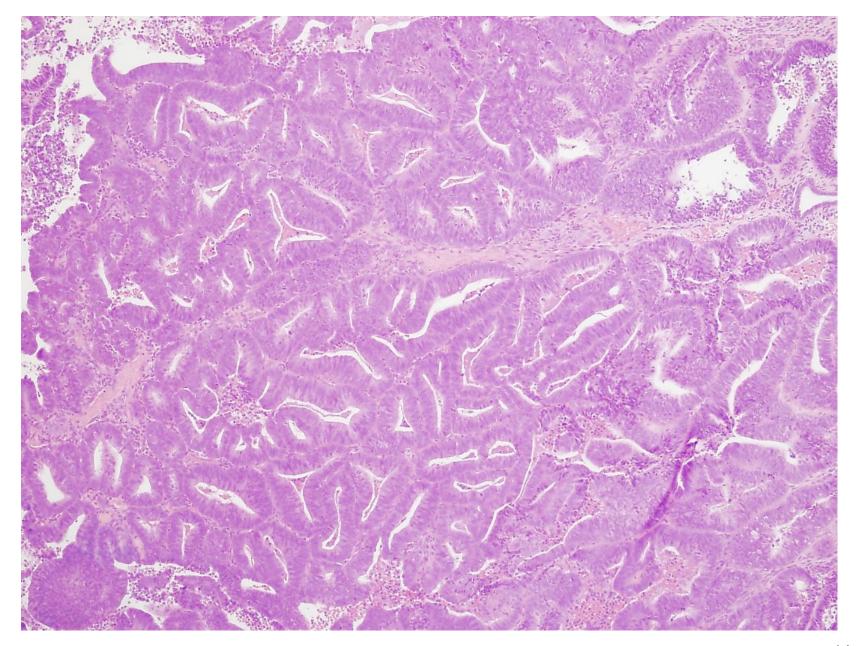
TNM FIGO Categories Stages			
TX			Primary tumour cannot be assessed
То			No evidence of primary tumour
T1		I <u>a</u>	Tumour confined to the corpus uteria
	T1a	IAª	Tumour limited to endometrium or invading less than half of myometrium
	T ₁ b	IB	Tumour invades one half or more of myometrium
T2		II	Tumour invades cervical stroma, but does not extend beyond the uterus
Т3		III	Local and/or regional spread as specified here:
	Тза	IIIA	Tumour invades the serosa of the corpus uteri or adnexae (direct extension or metastasis)
	T3b	IIIB	Vaginal or parametrial involvement (direct extension or metastasis)
N1,N2		IIIC	Metastasis to pelvic or para.aortic lymph nodes <u>b</u>
	N1	IIIC1	Metastasis to pelvic lymph nodes
	N2	IIIC2	Metastastis to para.aortic lymph nodes with or without metastasis to pelvic lymph nodes
T4 ^c		IV	Tumour invades bladder/bowel mucosa

TNM, 8th edition

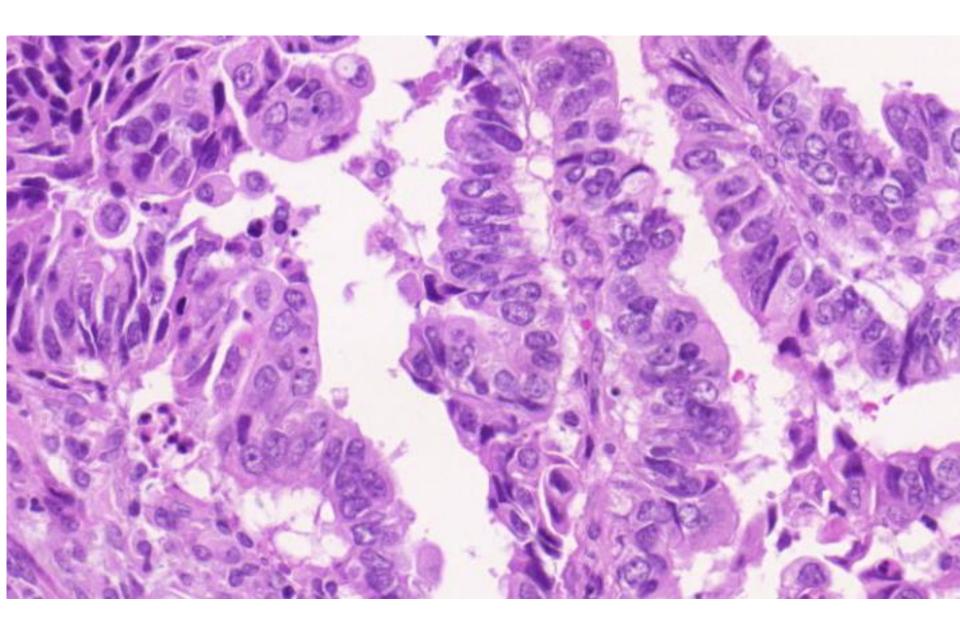




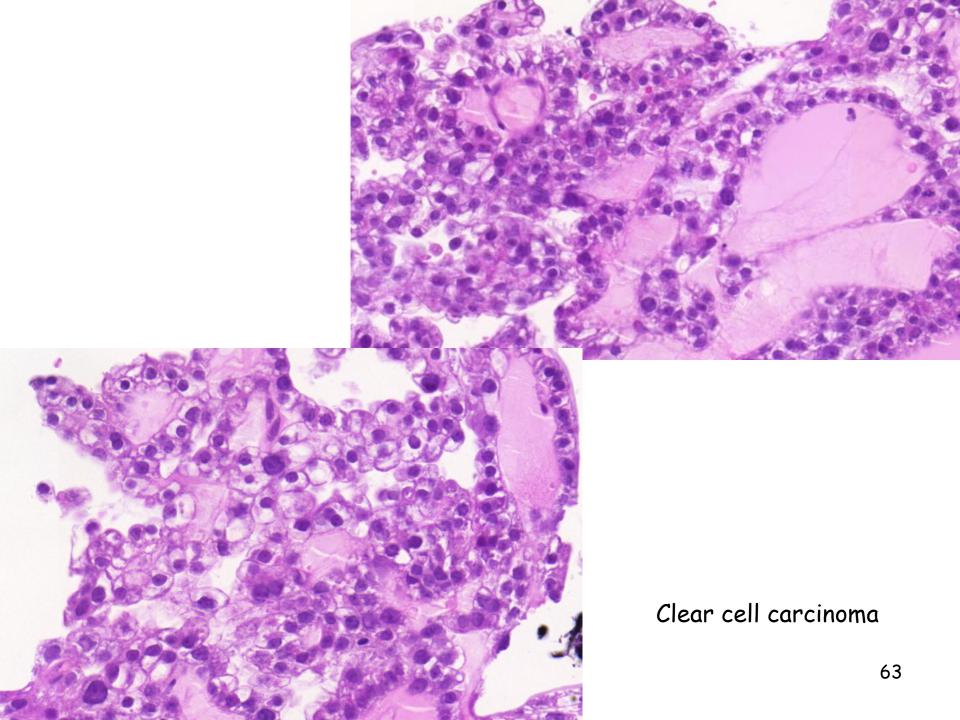




Endometrioid carcinoma



Papillary structures-high grade cytomorphology- Serous carcinoma



Tumors of the uterine corpus

Arising from		Benign	Malignant
Endometrium	Endometrial glands	-	Endometrioid carcinoma Serous cc Clear cell cc
	Endometrial stroma	Stromal nodule	Stromal sarcoma
	Endometrial glands and stroma	Adenofibroma Adenomyoma	Carcinosarcoma Adenosarcoma
Myometrium		Leiomyoma	Leiomyosarcoma

Endome	trial epithelial tumours and precursors Endometrial hyperplasia without atypia	8897/1 8891/1*	Smooth muscle tumour of uncertain malignant potenti Epithelioid smooth muscle tumour of uncertain
8380/2	Atypical hyperplasia of the endometrium		malignant potential
8380/3	Endometrioid adenocarcinoma NOS	8896/1*	Myxoid smooth muscle tumour of uncertain
0000/0	POLE-ultramutated endometrioid carcinoma		malignant potential
	Mismatch repair-deficient endometrioid carcinoma		Spindle smooth muscle tumour of uncertain
	p53-mutant endometrioid carcinoma		malignant potential
	No specific molecular profile (NSMP) endometrioid	8898/1	Metastasizing leiomyoma
	carcinoma	8890/3	Leiomyosarcoma NOS
8441/3	Serous carcinoma NOS		Spindle leiomyosarcoma
8310/3	Clear cell adenocarcinoma NOS	8891/3	Epithelioid leiomyosarcoma
8020/3	Carcinoma, undifferentiated, NOS	8896/3	Myxoid leiomyosarcoma
8323/3	Mixed cell adenocarcinoma	8930/0	Endometrial stromal nodule
9110/3	Mesonephric adenocarcinoma	8931/3	Endometrial stromal sarcoma, low grade
8070/3	Squamous cell carcinoma NOS	8930/3	Endometrial stromal sarcoma, high grade
8144/3	Mucinous carcinoma, intestinal type	8805/3	Undifferentiated sarcoma
9111/3*	Mesonephric-like adenocarcinoma	8590/1	Uterine tumour resembling ovarian sex cord tumour
8980/3	Carcinosarcoma NOS	8714/0	Perivascular epithelioid tumour, benign
0300/0	Carolinoal contact to o	8714/3	Perivascular epithelioid tumour, malignant
Tumour-	like lesions	8825/1	Inflammatory myofibroblastic tumour
	Endometrial polyp		Epithelioid myofibroblastic sarcoma
	Endometrial metaplasia		
	Arias-Stella reaction	6-200 March 200	pithelial and mesenchymal tumours
		8932/0	Adenomyoma NOS
Mesenc	nymal tumours specific to the uterus	8932/0	Atypical polypoid adenomyoma
8890/0	Leiomyoma NOS	8933/3	Adenosarcoma
8890/0	Lipoleiomyoma		
8890/0	Leiomyoma, apoplectic		ineous tumours
8890/0	Leiomyoma, hydropic	9473/3	Primitive neuroectodermal tumour NOS
8890/0	Dissecting leiomyoma	9064/3	Germ cell tumour NOS
8892/0	Cellular leiomyoma	9071/3	Yolk sac tumour NOS
8896/0	Myxoid leiomyoma	9080/0	Mature teratoma NOS
8891/0	Epithelioid leiomyoma	9080/3	Immature teratoma NOS
8893/0	Symplastic leiomyoma		
8890/1	Leiomyomatosis NOS		
8890/1	Intravenous leiomyomatosis		

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Endometrial stromal tumors

- · middle- aged (average 45 y) women
- tumor cells mimicking endometrial stromal cells

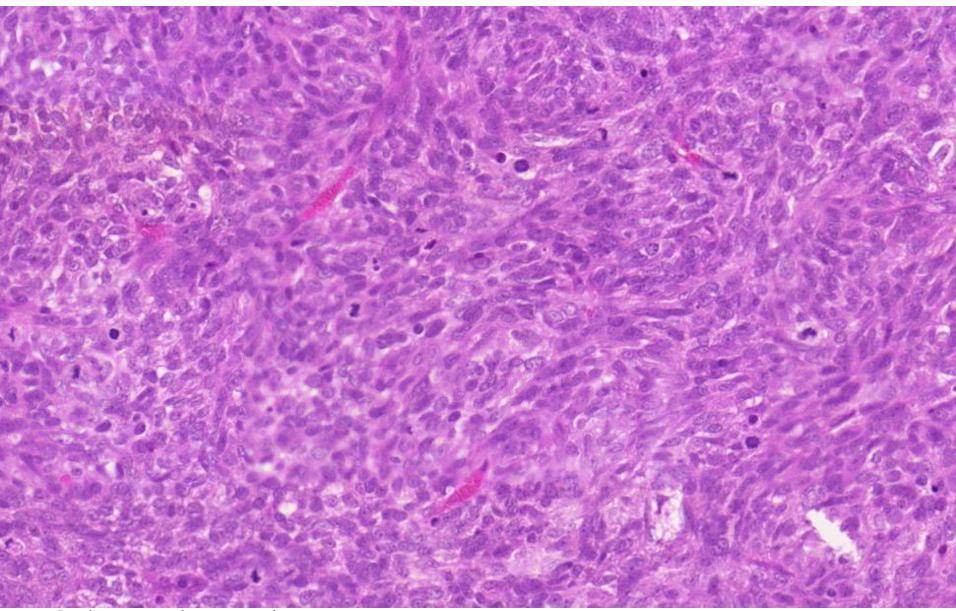
Endometrial stromal nodule



- · Endometrial stromal sarcomas
 - low and high grade group







Endometrial stromal sarcoma



Tumors of the uterine corpus

Arising from		Benign	Malignant
Endometrium	Endometrial glands	-	Endometrioid carcinoma Serous cc Clear cell cc
	Endometrial stroma	Stromal nodule	Stromal sarcoma
	Endometrial glands and stroma	Adenofibroma Adenomyoma	Carcinosarcoma Adenosarcoma
Myometrium		Leiomyoma	Leiomyosarcoma

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Tumour-	-like lesions	8825/1	Inflammatory myofibroblastic tumour
	Endometrial polyp		Epithelioid myofibroblastic sarcoma

Endometrial polyp Endometrial metaplasia Arias-Stella reaction

Mesenchymal tumours specific to the uterus

Meserici	lymai tumours specific to the
8890/0	Leiomyoma NOS
8890/0	Lipoleiomyoma
8890/0	Leiomyoma, apoplectic
8890/0	Leiomyoma, hydropic
8890/0	Dissecting leiomyoma
8892/0	Cellular leiomyoma
8896/0	Myxoid leiomyoma
8891/0	Epithelioid leiomyoma
8893/0	Symplastic leiomyoma
8890/1	Leiomyomatosis NOS
8890/1	Intravenous leiomyomatosis
	7.3

Mixed epithelial and mesenchymal tumours

WILL CO C	old for a file of the file of
8932/0	Adenomyoma NOS
8932/0	Atypical polypoid adenomyoma
8933/3	Adenosarcoma

Miscellaneous tumours

9473/3	Primitive neuroectodermal tumour NOS
9064/3	Germ cell tumour NOS
9071/3	Yolk sac tumour NOS
9080/0	Mature teratoma NOS
9080/3	Immature teratoma NOS

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Mixed epithelial and mesenchymal tumors

- Adenomyoma
- · Atypical polypoid adenomyoma
- · Adenofibroma
- · Adenosarcoma
- Carcinosarcoma (formerly malignant mixed müllerian tumor, now it is considered epithelial in origin with EMT)



Carcinosarcoma

- postmenopausal patients
- · uterine enlargement and bleeding
- · MA: large, soft, polypoid masses
- MI: admixture of carcinoma and sarcoma-like elements
 - carcinoma: high grade, undifferentiated, necrosis, hemorrhage
 - sarcoma: homologous or heterologous (skeletal muscle, cartilage, bone or fat)
- now it is considered epithelial in origin with EMT



Adenosarcoma

- generally regarded as low grade
- MA: large polypoid growth filling the uterine cavity
- MI: abnormally shaped glands (but no cytologic atypia!) and malignant stroma (the whole resembling phyllodes tumor of the breast)

Myometrium

Tumors of the uterine corpus

Arising from		Benign	Malignant
Endometrium	Endometrial glands	-	Endometrioid carcinoma Serous cc Clear cell cc
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Tumour-like lesions

Endometrial polyp Endometrial metaplasia Arias-Stella reaction

Mesenchymal tumours specific to the uterus

moderiorijina tamene epitemi		
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8891/0	Epithelioid leiomyoma	
8893/0	Symplastic leiomyoma	
8890/1	Leiomyomatosis NOS	
8890/1	Intravenous leiomyomatosis	
	*	

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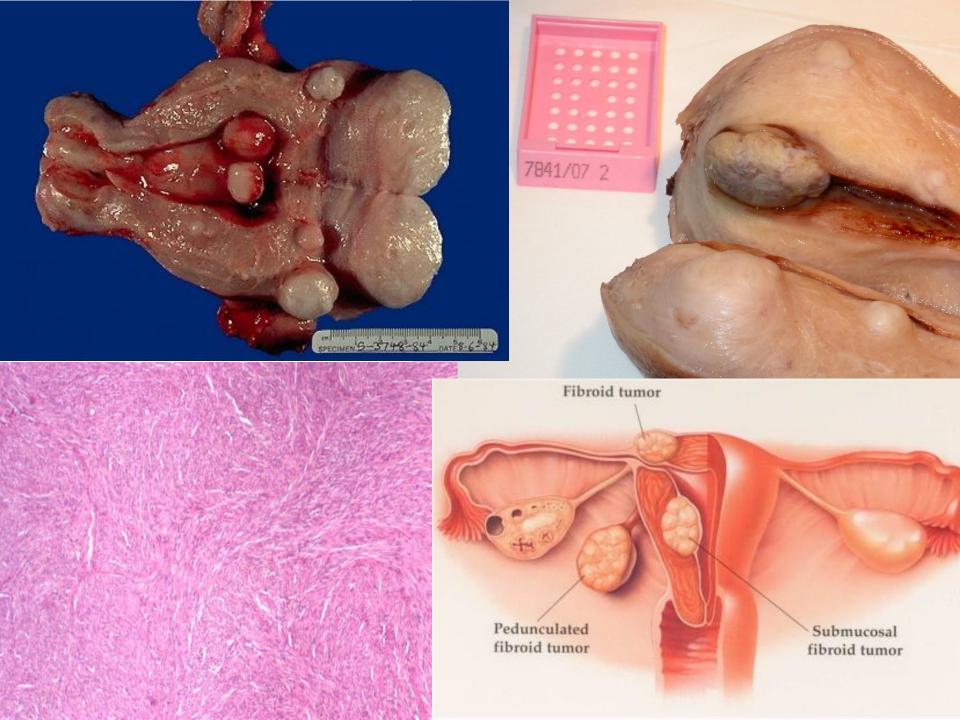
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Tumors of the Myometrium

Leiomyoma

- in 40% of women over the age of 50 years
- location: submucosal, intramural, subserosal
- **symptoms**: abnormal bleeding, pain, spontaneous abortion, impaired fertility, compression of the urinary bladder (frequency)
- MA: well circumscribed, round, grayish-whitish nodule(s) with a whorling pattern
- MA: uniform spindle shaped cells, no atypia, scanty mitoses



Jumors of the Myometrium

Leiomyosarcoma

- in older patients (average 55 years)
- MA: fleshy with necrosis and hemorrhage
- MI: hypercellular, nuclear atypia, pleomorphism, increased mitotic index, atypical mitoses, necrosis
- Metastases: pelvis, lung, bone, brain but lymph node metastases exceptional!



