Uterus

Abnormal uterine bleeding (AUB): Clinical term
Bleeding outside the menstrual cycle (abnormal)
bleeding or spotting between periods
bleeding after sex
abnormally heavy periods or irregularity in timing of periods
Metrorrhagia (irregular bleeding between the periods)
Menorrhagia (profuse (heavy) or prolonged bleeding at the time of the period)
In postmenopausal women: any bleeding is considered AUB "Postmenopausal bleeding"
In postmenopausal women, there is no bleeding because there is no estrogen or progesterone, so there is no proliferative or secretory changes. Therefore, any bleeding is considered abnormal. If bleeding occurs, it may be due to endometrial atrophy, where the endometrium becomes thin and inactive, and this condition is called atrophic inactive endometrium
Can affect women of any age, but especially at menarche, perimenopause or after menopause
Normal endometrial bx finding: **Reproductive age:** Menstrual phase. Proliferative endometrium. Secretory endometrium. **Postmenopausal:** Atrophic/inactive endometrium.
Biopsy is taken to exclude significant pathology (e.g., endometrial polyp, endometrial hyperplasia, endometrial carcinoma, leiomyoma, adenomyosis, stromal tumors, endometritis, exogenous hormone effects, pregnancy related bleeding). -> If significant underlying pathology has been exclude, then the diagnosis is dysfunctional uterine bleeding. A 35-year-old female patient came to us with menorrhagia. We performed a biopsy that showed a proliferative phase endometrium. When we looked at the last menstrual cycle, it was normal and consistent with the biopsy phase. So, what is the cause of the abnormal bleeding here? This is called abnormal uterine bleeding (AUB) functional type. Obviously, there is no evidence of hormonal abnormalities, and the likely cause is anovulation with increased estrogen levels Abnormal bleeding from the uterus in the **absence of an organic uterine lesion** = Dys**functional** uterine bleeding

Age Group	Cause(s)
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle
Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy) Proliferations (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma) Anovulatory cycle Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopause	Anovulatory cycle Irregular shedding Proliferations (carcinoma, hyperplasia, polyps)
Postmenopause	Proliferations (carcinoma, hyperplasia, polyps) Endometrial atrophy

Dysfunctional uterine bleeding:
Abnormal bleeding from the uterus in the absence of an organic uterine lesion

The most common cause of dysfunctional uterine bleeding is anovulation (failure to ovulate). Anovulatory cycles result from hormonal imbalances and are most common at menarche and in the perimenopausal period because of fluctuations in the hypothalamus/pituitary/ovarian axis.

They also happen due to:
(1) Endocrine disorders, such as thyroid disease, adrenal disease, or pituitary tumors
(2) Ovarian lesions, such as a functioning ovarian tumor (granulosa cell tumors) or polycystic ovarian syndrome
(3) Generalized metabolic disturbances, such as obesity, malnutrition, or other chronic systemic disorders

Dysfunctional uterine bleeding also may result from an inadequate luteal phase (an ovulatory cycle), which is thought to stem from insufficient production of progesterone by the corpus luteum. We have progesterone production, but it is not adequate to oppose the effect of estrogen on the endometrium

In postmenopausal women, the most common cause is atrophy, with bleeding from fragile vessels in the thinned endometrium.

In young females drugs, could be due to blood disorders or anticoagulants use

Endometriosis HY
Is defined by the presence of endometrial glands and stroma in a location outside the uterus
It occurs in as many as 10% of women in their reproductive years and in nearly 50% of women with infertility
Peak incidence, 30 - 45 years of age (reproductive years) can also be diagnosed at 20 years, any postpubertal/menstrauting women
Four hypotheses have been put forth to explain the origin of dispersed endometriotic lesions, all of which are viable
The regurgitation theory, which is currently favored, proposes that menstrual backflow through the fallopian tubes leads to implantation
The benign metastases theory holds that endometrial tissue from the uterus can “spread” to distant sites via blood vessels and lymphatics
The metaplastic theory, on the other hand, posits endometrial differentiation of coelomic epithelium (mesothelium of pelvis and abdomen from which endometrium originates) as the source
The extrauterine stem/progenitor cell theory, proposes that circulating stem/progenitor cells from the bone marrow differentiate into endometrial tissue
As compared to normal endometrium, endometriotic tissue exhibits increased levels of inflammatory mediators, particularly prostaglandin E2 (continues below)*
It is proposed that the inflammation results from the recruitment and activation of macrophages by factors made by endometrial stromal cells (...)
Stromal cells also make aromatase, leading to local production of estrogen (...)
These factors enhance the survival and persistence of the endometriotic tissue within a foreign location (a key feature in the pathogenesis of endometriosis) (...)
And help to explain the beneficial effects of COX-2 inhibitors and aromatase inhibitors in the treatment of endometriosis*
Endometriosis typically consists of functioning abnormal misplaced endometrium tissue, which undergoes cyclic bleeding
Because blood collects in these aberrant foci, they appear grossly as red-brown nodules or implants
They range in size from microscopic to 1 to 2 cm in diameter and lie on or just under the affected serosal surface.
Often, individual lesions coalesce to form larger masses
When the ovaries are involved (**67%**), the lesions may form large, blood-filled cysts that turn brown (chocolate cysts) as the blood ages
Development of malignant neoplasm occurs in <**1%** of cases (pre/postmenopause); **75%** of malignant neoplasms arise in ovarian endometriosis
So endometriosis is NOT a precursor lesion for that cancer
Endometrioid Tumors, they sometimes develop in association with endometriosis (1-**15%**), and that they are most commonly malignant
NOTE: ENDOMETRIODOSIS ALOMST HAS THE SAME GENETIC MUTATIONS PROFILE CHANGES AS THE ENDMETRIOD CARCINOMA BUT THE ENDOMETRIOD CARCINOMA DOES NOT DIRECLTY GET OUT OR ARISE FROM THE ENDOMETRIUM BUT ACTUALLY FROM THE OVARY
Endometriosis is associated with **ovarian clear cell carcinoma** and **ovarian endometrioid carcinoma** (mc) and shares **similar molecular alterations**
Endometriosis in patients **without cancer harbors oncogenic mutations in ARID1A** (mc/ tumor **suppressor** gene)
It is frequently multifocal and often involves pelvic structures (ovaries (MC), pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum)
Less frequently, distant areas of the peritoneal cavity or periumbilical tissues are involved
Uncommonly, distant sites such as lymph nodes, lungs, and even heart, skeletal muscle, or bone are affected
Appear around fibrotic areas like C-sections
With seepage and organization of the blood, widespread fibrosis occurs, leading to adhesions among pelvic structures, sealing of the tubal fimbriated ends, and distortion of the fallopian tubes and ovaries
Symptoms, depend on the distribution of the lesions
Extensive scarring of the fallopian tubes and ovaries often produces discomfort in the lower abdomen and eventual infertility

Endometriosis HY
Rectal wall involvement may produce pain on defecation (rectovaginal septum)
Involvement of the uterine or bladder serosa can cause dyspareunia (painful intercourse) and dysuria, respectively
The main manifestation is severe pain during menstruation, which is characteristic of dysmenorrhea
They typically have regular menses
So, almost all cases feature severe dysmenorrhea and pelvic pain resulting from intrapelvic bleeding and intraabdominal adhesions/pelvic pain
The diagnosis depends on finding of: endometrial tissue consisting of at least 2 of the following: endometrial type glands, endometrial type stroma or evidence of chronic hemorrhage (hemosiderin laden macrophages -> GOLDEN CELL)
Laparoscopy **surgical** direct visualization of pelvic/abdominal cavity, while the colposcopy was for the visual inspection of **cervix/vagina/vulva** after abnormal Pap smear

Condition	Description	Key Location/Feature
Adenomyosis	Endometrial glands & stroma *within the myometrium* (muscle of uterus)	Diffusely enlarged, "boggy" uterus; painful, heavy periods
Endosalpingiosis	Ectopic **fallopian tube-like epithelium** (ciliated columnar cells) outside fallopian tubes	Often found in pelvic peritoneum, ovaries; typically asymptomatic
Endocervicosis	Presence of **endocervical-type mucinous epithelium** in ectopic locations	Usually bladder wall or pelvic tissue; mucin-secreting columnar cells
Endometrioma	In the ovaries (**Ovarian endometriosis**)	Sectioning of ovary shows a large endometriotic cyst with degenerated blood (“chocolate cyst”)

Proliferative lesions of the endometrium and myometrium
Endometrial hyperplasia
Endometrial carcinomas
Endometrial polyps
Smooth muscle tumors
All tend to produce abnormal uterine bleeding as their earliest manifestation

Aspects	Endometrial Hyperplasia 4.5.6	Endometrial Carcinoma	Endometrial Polyps	Leiomyoma(s)/fibroid(s) (benign)	Leiomyosarcoma (malignant)
Age	Fourth to sixth decades (peak fifth)	55-65 years and is uncommon before age 40	Although endometrial polyps may occur at any age, they are most common around the time of menopause Most commonly benign Most arise in the **fundus** and are attached by a **sessile** or **pedunculated** stalk.	Reproductive age 30-50% Leiomyomas are the most common benign tumor in females conversely, these tumors shrink postmenopausally Estrogen sensitive(but not initiative, mutations are); tumor size increases with pregnancy and decreases with menopause.	Most often occur in postmenopausal women

Aspects	Endometrial Hyperplasia 4.5.6	Endometrial Carcinoma	Endometrial Polyps	Leiomyoma(s)/fibroid(s) (benign)	Leiomyosarcoma (malignant)
Description	Hyperplasia without atypia: carries a low risk (between 1% and 3%) for progression to endometrial carcinoma. No dysplasia, characterized by nests of closely packed glands. gland to stroma ratio is > 3:1 gland proliferation Hyperplasia with atypia: also called endometrial intraepithelial neoplasia (EIN), is associated with a much higher risk of progression to carcinoma (20%–50%).with dysplasia, gland to stroma ratio is > 3:1	**In the United States and many other Western countries, endometrial carcinoma is the most frequent cancer occurring in the female genital tract** Endometrial carcinoma can be broadly divided into two histologically and pathogenically distinct categories:- **Endometrioid carcinoma.** **Serous carcinoma.** There are other less common types of endometrial carcinoma, such as **Clear cell carcinoma** **Mixed Mullerian tumor (carcinosarcoma).** Closely resemble normal endometrium Are graded 1 to 3, based on the degree of differentiation; 3 tier system developed by the International Federation of Gynecology and Obstetrics (FIGO): FIGO 1 FIGO 2 FIGO 3 (RECALL THE OTHER SYSTEMS FOR GRADING HERE ↗ GRADING SYSTEMS FOR DIFFRENT CANCER)	These polyps are usually sessile and range from 0.5 to 3 cm in diameter Larger polyps may project from the endometrial mucosa (basalis) into the uterine cavity They are composed of endometrium resembling the basalis, frequently with small muscular arteries. Some glands are normal architecturally, but more often they are cystically dilated Their main clinical significance is that they may produce abnormal uterine bleeding	Benign tumors that arise from the smooth muscle cells in the myometrium Sharply circumscribed, firm graywhite masses with a characteristic whorled cut surface They may occur singly, but more often occur as multiple tumors that are scattered within the uterus, ranging from small nodules to large tumors that may dwarf the uterus Intramural: Embedded within the myometrium. Submucosal: Lie immediately beneath the endometrium. **Subserosal**: Lie immediately beneath the serosa (subserosal) In this **location**, tumors may extend out on attenuated stalks and even become attached to surrounding organs, from which they may develop a blood supply (**parasitic leiomyomas**). On histologic examination, the tumors are characterized by bundles of smooth muscle cells mimicking the appearance of normal myometrium. Foci of fibrosis, calcification, and degenerative softening may be present Leiomyomas of the uterus often are asymptomatic, being discovered incidentally on routine pelvic examination The most frequent presenting sign is menorrhagia, **with or without METRorrhagia** Submucosal fibroids in particular can cause prolonged and/or heavy	Leiomyosarcomas of the uterus virtually always arise **de novo** from the mesenchymal cells of the myometrium **NOT FROM THE LEIMYOMA** Soft, hemorrhagic, necrotic masses The diagnostic features of leiomyosarcoma include tumor necrosis, cytologic atypia, and mitotic activity Because increased mitotic activity is sometimes seen in benign smooth muscle tumors, particularly in young women, an assessment of all three features is necessary to make a diagnosis of malignancy Recurrence after surgery is common with these cancers, and many metastasize, typically to the lungs, yielding a 5-year survival rate of about 40%

Aspects	Endometrial Hyperplasia 4.5.6	Endometrial Carcinoma	Endometrial Polyps	Leiomyoma(s)/fibroid(s) (benign)	Leiomyosarcoma (malignant)
				menstrual bleeding. -/+ UTI Leiomyomas rarely, if ever, transform into sarcomas, and the presence of multiple lesions does not increase the risk of malignancy	
Cause	The cause is excessive estrogen effect, which can be endogenous or exogenous, such as hormone treatments like estrogen-only pills An excess of estrogen relative to progestin, if sufficiently prolonged or marked, can induce exaggerated endometrial proliferation (hyperplasia), which is an important precursor of endometrial carcinoma A COMMON cause of estrogen excess is obesity, as adipose tissue converts steroid precursors into estrogens Anovulation → ↓ progesterone → unopposed estrogen → hyperplasia risk Anovulatory or “disordered” endometrium containing dilated glands. Due to hormonal imbalance Prolonged administration of estrogenic steroids without counterbalancing progestin. Estrogen supplementation: systemic therapy to alleviate symptoms of menopause, Tamoxifen : hormonal treatment for breast cancer acts as estrogen receptor antagonist in breast but agonist in endometrium Estrogen-producing ovarian lesions (such as polycystic ovary syndrome and granulosa-theca cell tumors of the ovary).----	Estrogen excess in the setting of endometrial hyperplasia in perimenopausal women		Estrogens and possibly oral contraceptives stimulate the growth of leiomyomas	

Aspects	Endometrial Hyperplasia 4.5.6	Endometrial Carcinoma	Endometrial Polyps	Leiomyoma(s)/fibroid(s) (benign)	Leiomyosarcoma (malignant)
	increased circulating androgens peripherally converted into estrogen				
Genes	Inactivation of the PTEN tumor suppressor gene has been identified at a substantial frequency in hyperplasia with atypia (approximately 50%) and endometrioid carcinoma (>70%)	Mutations (inactivation) in mismatch repair genes (MMR deficient) and the tumor suppressor gene PTEN are early events in the stepwise development of endometrioid carcinoma	The stromal cells are monoclonal, often with a rearrangement of chromosomal region 6p21, and thus constitute the neoplastic component of the polyp	Chromosomal abnormalities: e.g. rearrangements of chromosomes 6 and 12 that also are found in a variety of other benign neoplasms, such as endometrial polyps and lipomas Mutations in the MED12 gene, which encodes a component of the RNA polymerase transcription complex, have been identified in up to **70**% of leiomyomas	
Treatment	When hyperplasia with atypia is discovered, it must be carefully evaluated for the presence of cancer and usually warrants a hysterectomy in patients no longer desiring fertility In younger patients, treatment with high-dose progestins may be used in an attempt to preserve the uterus	Surgical			

Serous cancers	Endometrioid cancers
Arise in the setting of endometrial atrophy in older **postmenopausal** women Irregular or postmenopausal bleeding.	Estrogen excess in the setting of endometrial hyperplasia in **perimenopausal** women Irregular or postmenopausal bleeding.
atypia without hyperplasia	atypia with hyperplasia
Is not associated with unopposed estrogen or endometrial hyperplasia	Is associated with unopposed estrogen or endometrial hyperplasia
Less common but also far more aggressive------15% of tumors	Accounts for 80% of cases of endometrial carcinomas Endometrioid carcinoma usually is slow to metastasize, but if left untreated, eventually disseminates to regional nodes and more distant sites
Nearly all cases of serous carcinoma have mutations in the TP53 tumor suppressor gene, whereas mutations in DNA mismatch repair genes and in PTEN are rare/late	Mutations (inactivation) in mismatch repair genes (MMR deficient) and the tumor suppressor gene PTEN are early events in the stepwise development of endometrioid carcinoma TP53 mutations occur but are relatively uncommon and are late events in the genesis of this tumor type **POLE gene mutation : better prognosis**

Serous cancers	Endometrioid cancers
Serous tumors are preceded by a lesion called serous endometrial intraepithelial carcinoma (SEIC) in which TP53 mutations are often detected Immunohistochemical staining shows accumulation of p53, a finding associated with TP53 mutation	Atypical endometrial hyperplasia / endometrioid intraepithelial neoplasia is regarded as the precursor lesion, in which PTEN mutations are often detected
	Risk factors for this type of carcinoma include (1) obesity, (2) diabetes, (3) hypertension, (4) infertility, and (5) exposure to unopposed estrogen. -----increased estrogenic stimulation of the endometrium Women with germline mutations in **PTEN** (Cowden Syndrome) (In GI hamartoma multiple GI polyps) and germline alterations in DNA **mismatch repair genes** (Lynch Syndrome) (Right sided colon cancer) are at high risk for this cancer So follow up with genetic testing to detect the ENDM cancer early
Typically grow in small **tufts** and **papillae** with marked cytologic atypia (SEROIOUS, SPIKES) They can also form glands that at times create confusion with endometrioid carcinoma, however serous carcinomas exhibit much greater cytologic atypia.	Glandular infiltrating the myometrium layer even in grade 1
By definition high grade	Depends on the FIGO grading system
Stage is the major determinant of **S**urvival in both types Serous carcinomas is strongly dependent on operative staging but because of its aggressive behavior it often presents as high-stage disease with a poor prognosis	**S**tage is the major determinant of **S**urvival in both types With therapy, the 5-year survival rate for early-stage endometrioid carcinoma is 90%, but survival drops precipitously in higher-stage tumors

GRADING SYSTEMS FOR DIFFRENT CANCER:

Cancer Type	Grading System	Structure	Notes
Prostate cancer	**Gleason grading system**	Scores from **6 to 10** (sum of 2 patterns, each graded 1–5)	Based on **glandular architecture**, not nuclear atypia. Higher score = worse.
Cervical cancer	**2-tiered SIL system**	**Low-grade SIL (LSIL)** and **High-grade SIL (HSIL)**	Replaces the older **CIN I/II/III** (3-tiered). Based on degree of dysplasia.
Endometrial cancer	**FIGO grading (Grade 1–3)**	Based on **glandular differentiation**: **Grade 1**: well diff (≤5% solid) **Grade 2**: mod (6–50%) **Grade 3**: poor (>50%) Endometrial carcinoma, Endometrioid type, grade 1, infiltrating myometrium and growing in a glandular pattern. Endometrial carcinoma, Endometrioid type, grade 3, has a predominantly solid growth pattern	FIGO = **International Federation of Gynecology and Obstetrics**
Breast cancer	BI-RADS Breast imaging-reporting and data system	Impressions on the behavioral of the tumour that is detected on the radiology using US, MRI for less than 1cm and for those with BC Hx and mammogram (1980s) for those who are old and are screening and those that has 1cm and larger masses	The higher the number the higher the malignancy 0,1,2,3 benign 4 likely malignant

Cancer Type	Grading System	Structure	Notes
			5 and 6 sus for malignancy so they have to be confirmed by histology

PCOS
Polycystic ovarian syndrome (PCOS) is a clinicopathologic syndrome comprising polycystic ovaries and characteristic clinical features Associated with endometrial hyperplasia and endometrial neoplasia
Polycystic ovaries resembling PCOS may be seen in prepubertal period or puberty without clinical manifestations
Enlarged, multicystic ovaries, although may not be enlarged in adolescent patients
Ovaries with multiple cysts, **hyperthecosis** and **atretic follicles**
Development of insulin resistance and hyperandrogenism in polycystic ovary disease is not fully understood
Familial clustering of cases has been observed, strongly suggesting a genetic basis for polycystic ovary disease, however, no specific genetic abnormality has been shown to be the sole culprit in the development of polycystic ovary disease
Menstrual disorders (from **amenorrhea** to menorrhagia)
Infertility, can be treated if hormonal imbalance is treated
Acne, **obesity**, hirsutism, **insulin** resistance and **diabetes**
Diagnostic criteria:- **Oligoovulation or anovulation** (biochemical signs hormonal assay).- **Excess androgen activity** (clinical or biochemical signs hormonal assay).- Polycystic ovaries **present** (by ultrasound)
Patients with **oligomenorrhea**, signs of **hyperandrogenism** (eg, acne, hirsutism), and infertility likely has polycystic ovary syndrome (PCOS). PCOS is characterized by increased ovarian androgen production, which acts on the hypothalamic-pituitary-ovarian (HPO) axis to cause an abnormally elevated LH/FSH ratio that inhibits ovulation. Therefore, a common presentation is irregular menses with anovulatory infertility. Obesity, which is common with PCOS, can also contribute to the anovulatory state by inducing **hyperinsulinism**, which acts synergistically in the ovary with **LH** to upregulate **androgen** production