PATHOLOGY OF THE FEMALE GENITAL SYSTEM

VULVA

VULVITIS

The most important infectious agents are
1. Human papillomavirus (HPV), producing condylomata acuminata and vulvar intraepithelial neoplasia
2. Herpes simplex genitalis (HSV 1 or 2), causing a vesicular eruption
3. Gonococci producing suppurative infection of the vulvovaginal glands
4. Syphilis, causing primary chancre at the site of inoculation
5. Candida causing vulvitis.

Contact Dermatitis is one of the most common causes of vulvar pruritus. It presents as erythematous weeping and crusting papules and plaques. Causes include urine, soaps, detergents, deodorants, etc.

NON-NEOPLASTIC EPITHELIAL DISORDERS (NNED) (previously vulvar dystrophies)

There are two forms of NNED 1. Lichen sclerosus and 2. Lichen simplex chronicus. Both appear clinically as a white lesion i.e. leukoplakia. The latter, however, has many other underlying conditions including, vitiligo, psoriasis, lichen planus, & carcinoma. Only biopsy and microscopic examinations can differentiate among these leukoplakias.

Lichen Sclerosus is characterized by thinning of the epidermis, hydropic degeneration of the basal cells, and dermal fibrosis. When the entire vulva is affected, the labia become atrophic with constriction of the vaginal orifice. It is most common in postmenopausal women. An autoimmune reaction is probably involved in its pathogenesis.

Lichen Simplex Chronicus is the end stage of many inflammatory dermatoses and is marked by epidermal hyperplasia and significant surface hyperkeratosis.

TUMORS

1. Condylomas and Low-Grade Vulvar Intraepithelial Neoplasia (VIN)

There are two biologic forms of anogenital warts (condylomas)

a. Condylomata lata: are manifestations of secondary syphilis & are flat, and slightly elevated. (Fig. 10-1)
b. Condylomata acuminata: are viral (HPV) warts and appear as elevated warty or flat & wrinkled localized lesions. They are often multiple, red-pink lesions that measure up to several centimeters in diameter. (Fig. 10-2)

Microscopically, there is acanthosis and hyper/parakeratosis, but koilocytosis. The latter are squamous cells with perinuclear cytoplasmic vacuoles and nuclear angulation. The koilocytes are characteristic of HPV infection. Condyloma acuminata are not precancerous but may coexist with foci of low-grade intraepithelial neoplasia in the vulva (VIN 1) and cervix. Indeed, VIN I and condylomas are both related to HPV 6 & 11 infections.

2. High-Grade VIN and Carcinoma of the Vulva

Carcinoma of the vulva is used to be seen mostly in elderly women. However, there has been an increase in the frequency of high grade VIN principally among younger women. The vast majority of vulvar carcinomas are of squamous type. Two biologic forms of vulvar carcinoma seem to exist

A. HPV-positive carcinoma (especially type 16) is seen in younger patients, particularly cigarette smokers. Many cases show coexisting carcinoma in situ, or condylomata acuminata.

B. HPV-negative carcinoma is seen in older women; frequently it is not associated with VIN.

VIN and early vulvar carcinomas appear as areas of leukoplakia due to epithelial thickening. These areas eventually transform into exophytic or ulcerative cancers. (Fig. 10-3)

Microscopic features: HPV-positive neoplasms tend to be poorly differentiated squamous cell carcinoma, whereas the HPV-negative lesions tend to be well-differentiated keratinizing. Ultimately, direct invasion with involvement of regional nodes and more distant spread occurs. Women with a tumor less than 2 cm in diameter have a much better prognosis than those with larger lesions.

3. Paget Disease of the vulva is a form of intraepithelial carcinoma. The majority of cases have no underlying carcinoma (cf. mammary Paget disease); it is considered as carcinoma of progenitor cells of the epidermis. The condition presents as a red, scaly, crusted plaque. Microscopically, large epithelial cells infiltrate the
epithelium, singly and in groups, with abundant granular cytoplasm and occasional cytoplasmic mucin vacuoles (Fig. 10-4)

**VAGINA**

**Congenital Anomalies** of the vagina are uncommon and include total absence of the vagina, a septate or double vagina.

**Vaginitis** is a relatively common problem that produces a vaginal discharge (leukorrhea).

Many of the offenders are normal commensals that become pathogenic in conditions such as diabetes, systemic antibiotic therapy, after abortion or pregnancy, or in AIDS. *Gonorrheal vaginitis* may occur and be transmitted to the newborn of the infected mother. *Candidal vaginitis* produces a curdy white discharge. *Trichomonas vaginalis* like candidiasis, is frequent, but produces a watery, profuse, gray-green discharge in which parasites can be identified microscopically. However, (like monilia) the infection can be asymptomatic.

**Non-specific atrophic vaginitis** is a common cause of postmenopausal bleeding. It is associated with thinning (atrophy) of the squamous vaginal mucosa. It is due to lack of estrogenic support of the vaginal epithelium.

**Malignant Tumors**

1. **Squamous cell carcinoma** is very rare & usually occurs in elderly women, with risk factors similar to those for cervical carcinoma. Vaginal intraepithelial neoplasia is a precursor lesion associated with HPV infection.

2. **Clear cell adenocarcinoma** usually affects adolescent and young females whose mothers took diethylstilbestrol during pregnancy. The tumor may arise from the cervix rather than the vagina in a third of the cases. Vaginal adenosis presents as red foci consisting of small glands lined by columnar cells; this is a benign condition from which the clear cell adenocarcinoma is thought to arise.

3. **Sarcoma botryoides** (embryonal rhabdomyosarcoma), produces soft polypoid masses and is usually seen in infants and children younger 5 years of age. (Fig. 10-5)

**THE CERVIX UTERI**

**Cervicitis** is a very common condition that is associated with a mucopurulent discharge. Cytologic examination of the discharge reveals inflamatory cells admixed with cervical epithelial cells, and possible microorganisms. It is often due to vaginal flora, streptococci, staphylococci, and *E. coli*. Much more important are *Chlamydia trachomatis*, *Ureaplasma*, *Trich. vaginalis*, *Candida spp.*, *Neisseria gonorrhoeae*, herpes simplex II (genitalis), and *HPV*. Many of these microorganisms are transmitted sexually, and so the cervicitis may represent a sexually transmitted disease. Among these pathogens, *C. trachomatis* is by far the most common sexually transmitted cervicitis. *Herpetic infections* of the cervix are important because the infection may be transmitted to the infant during its passage through the birth canal, sometimes resulting in a serious, sometimes fatal, systemic infection.

**Pathologic features**

Non-specific cervicitis may be either *acute* or *chronic*. Excluding gonococcal infection, the uncommon *acute nonspecific cervicitis* is limited to postpartum women and is usually caused by staphylococci or streptococci. *The chronic form is very common* and usually referred to as *nonspecific cervicitis*. Specific forms include *herpesvirus* ulcerative lesions and changes caused by *C. trachomatis*. Chronic cervicitis consists of inflammation and epithelial regeneration. These changes may occur in both squamous and columnar mucosa. Eventually, the columnar epithelium undergoes squamous metaplasia.

**Cervical Tumors**

Despite dramatic improvements in early diagnosis and treatment, cervical carcinoma continues to be one of the major causes of cancer-related deaths in women in the developing world.

**Cervical Intraepithelial Neoplasia (CIN)**

The Pap smear, introduced 50 years ago by Papanicolaou, remains the most successful cancer screening test ever developed. In populations that are screened regularly, cervical cancer mortality is reduced by up to 99%. Nearly all invasive cervical squamous cell carcinomas arise from precursor epithelial changes referred to as cervical intraepithelial neoplasia (CIN). Detection of CIN by the Pap smear at an early stage permits curative treatment. Cytological examination can detect CIN long before any abnormality can be seen grossly. CIN begins as low-grade lesion that may progress to higher grade CIN, or it is a high-grade lesions from the outset;
this depends on the location of the HPV infection in the transformation zone, the type of HPV infection (high versus low risk), and other host factors. 

On the basis of histology, precancerous changes are graded as:

- **CIN I**: Mild dysplasia
- **CIN II**: Moderate dysplasia
- **CIN III**: Severe dysplasia/carcinoma in situ

The current **Bethesda system** divides the precancerous lesions into only two groups:

1. **Low-grade SIL** (SIL for squamous intraepithelial lesions), equivalent to CIN I
2. **High-grade SIL**, Equivalent to CIN II & III

Progression from low- to high-grade SIL may or may not occur. The higher the grade of CIN the greater the likelihood of progression to invasive carcinoma, this reaches to 70% with CIN III.

**Epidemiology and Pathogenesis**

- The peak age of CIN incidence is about 30 years, whereas that of invasive carcinoma is about 45 years i.e. precancerous changes usually take many years to evolve into overt carcinomas.

- **Important risk factors for the development of CIN and invasive carcinoma are:**
  1. Early age at first intercourse
  2. Multiple sexual partners
  3. Persistent infection by "high-risk" papilloma viruses
  4. Low socio-economic status

- All of the above favor a sexually transmitted causative agent (HPV). Indeed, **HPV can be detected by molecular techniques in nearly all precancerous and cancerous lesions.** Specifically, **high-risk HPV types including 16 & 18**, account for the majority of cervical carcinomas. By contrast, condylomas, which are benign lesions, are caused by **low-risk HPV types** (i.e., 6 & 11). In these benign lesions the viral DNA does not integrate into the host genome.

- By contrast, **HPV types 16 & 18 usually integrate into the host genome with subsequent inactivation of the tumor suppressor genes p53 and RB.** The result is a transformed cell, capable of autonomous growth and susceptible to the acquisition of further mutations (cancer progression). **The recently introduced HPV vaccine is very effective in preventing HPV infections and hence cervical cancers.**

- Although many women harbor these viruses, only a few develop cancer, suggesting other pathogenetic influences play a role e.g. cigarette smoking and immunodeficiency states such as AIDS.

**Microscopic features**

- **CIN & Carcinoma in situ**
  
  - **CIN begins with CIN I.** This lesion is characterized by koilocytotic changes mostly in the superficial layers of the epithelium. **Koilocytosis** is composed of nuclear hyperchromasia and angulation with perinuclear vacuolization produced by cytopathic effect of HPV. The dysplastic epithelium is limited to the lower third of the mucosa.
  
  - **In CIN II** the dysplasia is more severe, involving the lower two-thirds of the mucosa. The superficial layer in some cases shows the koilocytotic changes.
  
  - **CIN III** shows dysplastic changes that affect virtually all layers of the epithelium. Surface cells and their koilocytotic changes are usually absent. (Figs. 10-6).
  
  - In time, dysplastic changes become more atypical and may extend into the endocervical glands, but the alterations are confined to the epithelial layer and its glands. These changes constitute **carcinoma in situ.**

- The next stage is **invasive carcinoma.**

The above progression sequences do not occur in all the cases.

**Cervical cytology and cervical colposcopy remain the basis of cervical cancer prevention.**

**Invasive Carcinoma of the Cervix**

The most common cervical carcinomas are (in descending order)

1. Squamous cell carcinomas (75%) 
2. Adenocarcinomas and adenosquamous carcinomas (20%) 
3. Small-cell neuroendocrine carcinomas (<5%)
The squamous cell carcinomas are increasingly appearing in younger women, (peak incidence at about 45 years); 10 to 15 years after detection of their precursors (CIN).

- Invasive carcinomas of the cervix develop in the region of the transformation zone (the squamo-columnar junction) and range from invisible microscopic foci of early stromal invasion to grossly visible exophytic ulcerating masses or deeply infiltrative cancer that encircle the os (Fig. 10-7 A).
- Tumors encircling the cervix and penetrating into the underlying stroma produce a "barrel cervix," which can be identified by direct palpation.
- Extension into the parametrial soft tissues can fix the uterus to the pelvic structures.
- Spread to pelvic lymph nodes is determined by tumor depth of invasion, ranging from less than 1% for tumors under 3 mm in depth to over 10% once invasion exceeds 5 mm.
- Three microscopic variants of cervical SCC squamous cell carcinoma exist, although admixtures and intermediate forms occur: (Fig. 10-7 B)
  1. Large cell nonkeratinizing
  2. Keratinizing
  3. Small cell; this should be distinguished from small cell neuroendocrine carcinoma
- Distant metastases, including para-aortic nodal involvement, remote organ involvement, or invasion of adjacent structures such as bladder or rectum, occur late in the course of disease.

With the exception of neuroendocrine tumors, which are uniformly aggressive, cervical carcinomas are graded from 1 to 3 based on the degree of cellular differentiation and staged from 1 to 4 depending on the extent of clinical spread.

Ideally cervical carcinomas should be diagnosed in the preinvasive phase; these appear as white areas on colposcopic examination after application of dilute acetic acid (Schiller test). More advanced cases of cervical cancer are invariably seen in women who either have never had a Pap smear or have waited many years since the prior smear. Such tumors call to attention by unexpected vaginal bleeding, leukorrhea, painful coitus (dyspareunia), and dysuria. Mortality is most strongly related to the tumor stage. The 5-year survival in stage 1 is 90% but this figure drops to 10% in stage 4.

**Endocervical Polyp**
This may protrude, sometimes, through the exocervix. The trend is to regard these polyps as inflammatory rather than neoplastic. They are generally small, soft, and have smooth, glistening surface and subjacent cystically dilated spaces filled with mucinous secretion.

**BODY OF UTERUS**

**Endometritis**
This may be associated with retained products of conception subsequent to miscarriage or delivery, or a foreign body such as an intrauterine device. Retained tissues or foreign bodies act as a nidus for infection, frequently by flora ascending from the vaginal or anal region. Endometritis is either acute or chronic depending on whether there is a predominant neutrophilic or lymphoplasmacytic response; however, components of both may be present in otherwise normal endometrium. *Generally the diagnosis of chronic endometritis requires the presence of plasma cells* (Fig 10-8). *Acute endometritis is frequently due to N. gonorrhoeae or C. trachomatis.* Microscopically, neutrophilic infiltrate in the superficial endometrium and glands coexists with a stromal lymphoplasmacytic infiltrate.

All forms of endometritis may present with menstrual abnormalities, infertility and ectopic pregnancy due to extension of the damaging inflammation to the fallopian tubes. Occasionally *tuberculosis* may present as granulomatous endometritis, frequently with tuberculous salpingitis and peritonitis. (Fig. 10-9)

**Adenomyosis**
This refers to the “*invagination of the stratum basalis of endometrium down into the myometrium.*” Nests of endometrial stroma, glands, or both, are found well down in the myometrium between the muscle bundles. The latter become hypertrophied. Accordingly, the uterine wall often becomes thickened and the uterus is enlarged and globular. (Fig. 10-10) Because these glands derive from the stratum basalis, they do not undergo cyclical
bleeding. Nevertheless, marked adenomyosis may produce menorrhagia, dysmenorrhea, and pelvic pain before the onset of menstruation.

Endometriosis
This is characterized by “the presence of endometrial glands and stroma in a location outside the endomyometrium.” It occurs in as many as 10% of women in their reproductive years and in nearly half of women with infertility. It may present as a pelvic mass filled with degenerating blood (chocolate cyst). It is frequently multifocal and may involve any tissue in the pelvis (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum), less frequently in more remote sites of the peritoneal cavity and about the umbilicus. Three possibilities have been suggested to explain the origin of these lesions.

1. **The regurgitation theory**, currently the most accepted, proposes menstrual backflow through the fallopian tubes with subsequent implantation.
2. **The metaplastic theory** proposes endometrial differentiation of coelomic epithelium.
3. **The vascular or lymphatic dissemination theory** has been raised to explain extrapelvic endometriosis.

Gross features
- Endometriosis almost always contains functioning endometrium, which undergoes cyclic bleeding. Because blood collects in these ectopic foci, they usually appear grossly as red-blue to yellow-brown nodules.
- They vary in size from microscopic up 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, the lesions may form large, blood-filled cysts that are transformed into so-called chocolate cysts as the blood ages (Fig. 10-11).
- Seepage and organization of the blood leads to widespread fibrosis, adherence of pelvic structures, sealing of the tubal fimbriated ends, and distortion of the oviducts and ovaries.

Microscopic features
- The histologic diagnosis depends on finding two of the following three features within the lesions:
  1. Endometrial glands
  2. Endometrial stroma, or
  3. Hemosiderin pigment.

Extensive scarring of the oviducts and ovaries often causes sterility. Pain on defecation reflects rectal wall involvement, and dyspareunia (painful intercourse) and dysuria reflect involvement of the uterine and bladder serosa, respectively. In almost all cases, there is severe dysmenorrhea and pelvic pain as a result of intrapelvic bleeding and periuterine adhesions.

Organic & Dysfunctional Uterine Bleeding
Menorrhagia, metrorrhagia, & postmenopausal bleeding are common complaints. Common organic causes include polyps, leiomyomas, endometrial carcinoma, endometrial hyperplasia, and endometritis, as well as cervical and vaginal lesions (polyps, cervicitis, or carcinoma).

Causes of Abnormal Uterine Bleeding by Age Group include
Prepuberty: precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence: anovulatory cycle
Reproductive age:
- complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy),
- Organic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma),
- anovulatory cycle,
- ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopause: anovulatory cycle, irregular shedding, Organic lesions (carcinoma, hyperplasia, polyps)
Postmenopause: Organic lesions (carcinoma, hyperplasia, polyps), endometrial atrophy

Dysfunctional Uterine Bleeding (DUB) is an abnormal bleeding in the absence of a well-defined organic lesion in the uterus. Examples of the causes of DUB include
- Anovulatory cycles are very common at both ends or reproductive life, and have several cause including
1. **Endocrine dysfunctions** e.g. of the hypothalamic-pituitary axis, adrenal, or thyroid
2. **Ovarian lesions producing an excess of estrogen**
3. **Malnutrition, obesity, or debilitating disease**
4. **Severe physical or emotional stress.**

Regardless of the cause, an anovulatory cycle leads to an excess of estrogen relative to progesterone; the endometrial glands may appear crowded with mild cystic changes with a relative scant stroma. (Fig. 10-12) The poorly supported endometrium partially collapses, with rupture of spiral arteries, accounting for the bleeding.

**Inadequate luteal phase.** The corpus luteum may fail to mature normally or may regress prematurely, leading to a relative lack of progesterone. The endometrium under these circumstances shows delay in the development of the secretory changes expected at the date of biopsy.

**Contraceptive-induced bleeding:** older oral contraceptives containing synthetic estrogens and progestin induced a variety of endometrial responses—for example, inactive, nonsecretory glands. The pills in current use have corrected these abnormalities.

### Endometrial Hyperplasia
This is an exaggerated endometrial proliferation induced by sufficiently prolonged excess of estrogen relative to progestin. The severity of hyperplasia is classified according to two parameters

a. architectural crowding of the glands &

b. cytologic atypia.

Accordingly there are three categories

1. Simple hyperplasia
2. Complex hyperplasia
3. Atypical hyperplasia

These three categories represent a spectrum based on the level and duration of the estrogen excess. The risk of developing carcinoma depends on the severity of the hyperplastic changes and associated cellular atypia. **Simple hyperplasia carries a negligible risk,** while **a woman with atypical hyperplasia has a 20% risk of developing endometrial carcinoma.** Thus **When atypical hyperplasia is discovered, it must be carefully evaluated for the presence of cancer and must be monitored by repeated endometrial biopsy.** Any estrogen excess may lead to hyperplasia.

**Potential contributors include**
1. **Failure of ovulation,** e.g. around the menopause
2. **Prolonged administration of estrogenic steroids**
3. **Estrogen-producing ovarian lesions such as**
   a. polycystic ovaries (Stein-Leventhal syndrome)
   b. cortical stromal hyperplasia
   c. granulosa-theca cell tumors of the ovary
4. **Obesity,** because adipose tissue processes steroid precursors into estrogens.

**Gross features**
- In simple hyperplasia the endometrium is diffusely thickened (Fig. 10-13)
- In complex & atypical hyperplasia there is usually focal thickening of the endometrium.

**Microscopic features**
- **Simple hyperplasia** involves both the glands & stroma; the normal gland to stroma ratio is maintained. The glands are proliferative and some are cystically dilated.
- **Complex hyperplasia:** there is glandular crowding with little stroma separating the proliferative glands. Typically, this is a focal process. (Fig. 10-14)
- **Simple and complex hyperplasias are further divided into atypical and non-atypical**
- **Atypical hyperplasia:** characterized by atypical nuclei of the proliferative glands as evidenced by nuclear stratification, nuclear rounding and the presence of nucleoli (Fig. 10-15)

### Tumors of the Endometrium and Myometrium
The most common neoplasms of the body of the uterus are
1. Endometrial polyps,
2. Smooth muscle tumors, and
3. Endometrial carcinomas.
All tend to produce bleeding from the uterus as the earliest manifestation.

**Endometrial Polyps** are usually sessile, hemispheric lesions up to 3 cm in diameter. Larger polyps tend to be pedunculated & may project from the endometrial mucosa into the uterine cavity & sometimes through the cervix into the vagina. **Microscopically**, they are composed of basalis-type, often cystically dilated glands with a rather fibroblastic stroma. Small muscular arteries are often prominent. The stromal cells have been found to be monoclonal. This signifies that they are the neoplastic component. The clinical significance of these polyps lies in the production of abnormal uterine bleeding and, more important, the risk (however rare) of giving rise to a cancer. (Fig. 10-16)

**Leiomyomas** are benign tumors that arise from the smooth muscle cells in the myometrium. Because of their firmness they are also called **fibroids**. They are the most common benign tumor in females and are found in 30% to 50% of women during reproductive life. Estrogens and possibly oral contraceptives stimulate their growth; conversely, they shrink postmenopausally.

**Gross features:**
- They are sharply circumscribed, firm gray-white masses with a characteristic whorled cut surface.
- They may occur singly, but are often multiple tumors scattered within the uterus, ranging in size from small seedlings to massive neoplasms that dwarf the size of the uterus.
- Some are embedded within the myometrium (*intramural*), whereas others may lie directly beneath the endometrium (*submucosal*) or directly beneath the serosa (*subserosal*). (Fig. 10-17 A)
- Larger neoplasms may show foci of ischemic necrosis with areas of hemorrhage and cystic softening (red degeneration)
- After menopause they may become densely collagenous and even calcified.

**Microscopic features**
- There are **whorling bundles of smooth muscle cells**.
- Foci of fibrosis, calcification, ischemic necrosis, cystic degeneration, and hemorrhage may be present. (Fig. 10-17 B)

Leiomyomas of the uterus may be entirely asymptomatic and be discovered only on routine pelvic examination or imaging studies. The most frequent manifestation, when present, is **menorrhagia**. Large masses in the pelvic region may become palpable or may produce a **dragging sensation**. Benign leiomyomas rarely transform into sarcomas.

**Leiomyosarcomas** typically arise de novo from the mesenchymal cells of the myometrium. They are almost always solitary tumors, in contradistinction to the frequently multiple leiomyomas.

**Gross features** (Fig. 10-18)
- The tumor is typically bulky
- It infiltrates the uterine wall.
- Some times it projects into the endometrial cavity.
- They are frequently soft, hemorrhagic, and necrotic.

**Microscopic features**
- They show a wide range of differentiation, from those that closely resemble leiomyoma to wildly anaplastic tumors.
- The diagnostic features of leiomyosarcoma include **tumor necrosis**, **cytologic atypia**, and **mitotic activity**. Since increased mitotic activity alone is sometimes seen in benign smooth muscle tumors in young women, an assessment of all three features is necessary to make a diagnosis of malignancy.

Recurrence after removal is common with these cancers, and many metastasize, typically to the lungs.
Endometrial Carcinoma (EMC)
After the dramatic drop in the incidence of cervical carcinoma, EMC is currently the most frequent cancer occurring in the female genital tract.

Epidemiology and Pathogenesis
EMC appears most frequently around the age of 60 years. There are two clinico-pathological settings in which endometrial carcinomas arise:
1. In perimenopausal women with estrogen excess; these are of endometrioid type
2. In older women with endometrial atrophy; these are of serous type.

Well-defined risk factors for endometrioid carcinoma include
a. Obesity: associated with increased synthesis of estrogens in fat depots
b. Diabetes
c. Hypertension
d. Infertility: women tend to be nulliparous, often with anovulatory cycles.

At least some of these risk factors point to increased estrogen stimulation, and indeed it is well recognized that prolonged estrogen replacement therapy and estrogen-secreting ovarian tumors increase the risk of this form of cancer. Many of these risk factors are the same as those for endometrial hyperplasia, and endometrial carcinoma frequently arises on a background of endometrial hyperplasia. Mutations in DNA mismatch repair genes and PTEN have been demonstrated. Serous carcinoma of the endometrium typically arises in a background of atrophy. Nearly all cases have mutations in the p53 tumor suppressor gene.

Gross features
- EMC may be exophytic (fungating, polypoid) or infiltrative. (Fig. 10-19 A)

Microscopic features
- The endometrioid carcinoma consists of malignant endometrial-like tubular glands of varying grades. Squamous metaplasia is frequent. Sometimes, the tumor is adeno-squamous carcinoma. (Fig. 10-19 B)
- Tumors originate in the mucosa and may infiltrate the myometrium and enter vascular spaces, with metastases to regional lymph nodes.
- Serous carcinoma forms small tufts and papillary arrangements rather than the glands seen in endometrioid carcinoma, and has much greater cytologic atypia. They are particularly aggressive (Fig. 10-19 C).

Patients with EMC presents with leukorrhea and irregular bleeding. With progression, the uterus may become palpable, and in time it becomes fixed to surrounding structures by extension of the cancer beyond the uterus. EMCs are usually late-metastasizing neoplasms, but dissemination eventually occurs, with involvement of regional nodes and more distant sites. The prognosis depends heavily on the stage of the disease.

FALLOPIAN TUBES
Salpingitis is inflammations of the tube and is almost always microbial in origin. With the declining incidence of gonorrhea, nongonococcal organisms, such as Chlamydia, Mycoplasma hominis, coliforms, and (in the postpartum setting) streptococci and staphylococci, are now the major offenders. Compared to gonococci, the nongonococcal infections differ in that they are more invasive, penetrating the wall of the tubes and thus tend more often to give rise to blood-borne infections and seeding of the meninges, joint spaces, and sometimes the heart valves. Tuberculous salpingitis is far less common and is encountered almost always in combination with tuberculosis of the endometrium.

All forms of salpingitis may produce pelvic masses when the tubes become distended with either exudate or, later, burned-out inflammatory debris and secretions. Adherence of the tube to the ovary and adjacent ligamentous tissues results in a tubo-ovarian abscess, (Fig. 10-20) or when infection subsides, a tubo-ovarian complex. Even more serious is the potential for adhesions that increases the risk of tubal ectopic pregnancy. Damage or obstruction of the tubal lumina may produce permanent sterility.

Tubal pregnancy (see later) (Fig. 10-21)
Primary adenocarcinomas of the fallopian tubes may be of papillary serous or endometrioid histology and frequently involve the omentum and peritoneal cavity at presentation.

OVARIES
Follicle cyst and Luteal Cyst are common and usually harmless lesions originate in unruptured graafian follicles or in follicles that have ruptured and immediately sealed. Such cysts are often multiple and subserosal. Occasionally, they achieve diameters of 4 to 5 cm and may thus become palpable and produce pelvic pain. They may also rupture, producing intraperitoneal bleeding and acute abdominal symptoms. (Fig. 10-22)

Polycystic Ovaries (Stein-Leventhal syndrome)
Oligomenorrhea, hirsutism, infertility, and sometimes obesity may appear in young women secondary to excessive production of androgens by multiple cystic follicles in the ovaries. The ovaries are usually twice the normal size, gray-white with a smooth outer surface, & studded with subcortical cysts 0.5 to 1.5 cm in diameter. Microscopically, there is a thickened, fibrotic tunica with underlying follicular cysts. Stigmata of previous ovulation are usually absent (corpora lutea or albicans). (Fig. 10-23) In most patients there are excessive production of androgens, high concentrations of luteinizing hormone, and low concentrations of follicle-stimulating hormone. These changes inhibit ovulation. It is proposed that the ovaries in this condition elaborate excess androgens and these, through the hypothalamus, inhibit the secretion of follicle-stimulating hormone by the pituitary. The basis of excess ovarian androgen secretion is not clear. The diagnosis of this syndrome cannot be made on morphological grounds alone; both clinical & endocrine data are also required.

TUMORS OF THE OVARY
Ovarian cancer is the fifth leading cause of cancer death in women. Tumors of the ovary are diverse and this diversity is attributable to the three cell types that make up the normal ovary:
1. The surface (coelomic) covering epithelium
2. The germ cells
3. The sex cord/stromal cells.
Each of these cell types gives rise to a variety of tumors (Fig. 10-24). Neoplasms of surface epithelial constitute the great majority of primary ovarian tumors (70%), and their malignant forms account for 90% of ovarian cancers. Germ-cell and sex cord/stromal cell tumors constitute 20% to 30% of ovarian tumors, but are collectively responsible for fewer than 10% of malignant tumors.

Pathogenesis
Nulliparity and family history are the two most important risk factors of epithelial ovarian cancers. There is a higher incidence of carcinoma in unmarried women and married women with low parity. Up to 10% of ovarian cancers are familial; the majority of these hereditary cancers seem to be caused by mutations in BRCA1 and BRCA2 genes, these are also associated with hereditary breast cancer. Indeed, with mutations in these genes there is increased risk for both ovarian and breast cancers. Mutations in BRCA genes are also present in 10% of sporadic (nonfamilial) ovarian cancers. Other molecular changes of ovarian neoplasms include HER2/NEU & K-RAS proteins over-expression and p53 mutation. The latter is present in about 50% of all ovarian cancers.

Surface Epithelial Tumors
These neoplasms are derived from the surface coelomic mesothelial covering of the ovary. With repeated ovulation and scarring the surface epithelium is pulled into the subjacent cortex, forming small epithelial cysts. These can undergo metaplasia with subsequent neoplastic transformation into the various histological types of the epithelial tumors. Benign lesions are usually cystic (cystadenoma) or can have an accompanying stromal component (cystadenofibroma). Malignant tumors may also be cystic (cystadenocarcinoma) or solid (carcinoma). The surface epithelial tumors also have an intermediate, borderline category referred to as tumors of low malignant potential. These seem to be low-grade cancers with limited invasive potential. Thus, they have a better prognosis than the fully malignant ovarian carcinomas. Surface epithelial tumors are divided into serous, mucinous, endometrioid & Brenner tumors.

A. Serous Tumors are the most frequent of the ovarian tumors. Combined, borderline and frankly malignant serous carcinomas are the most common malignant ovarian tumors (60% of all ovarian cancers). Benign lesions are usually encountered around 35 years of age, and malignant ones around 55.

Gross features
- Most serous tumors are large, spherical, and cystic.
- About 25% of the benign forms are bilateral. These benign tumors display a smooth and glistening serosal covering.
They are generally unilocular, but larger examples may be multilocular.

The cystic spaces are usually filled with a clear serous fluid.

Projecting into the cystic cavities are papillary projections that become more marked in malignant tumors. (Fig. 10-25)

In contrast to the benign examples, the surface of cystadenocarcinoma shows nodular or warty irregularities that represent cancerous penetration of the serosa. (Fig. 10-26)

**Microscopic features**

The benign tumors show a single layer of tall columnar epithelium that lines the cyst(s).

Psammoma bodies (rounded laminated calcified structures) are common.

In carcinoma, the lining cells display malignant features with invasion of the stroma. Papillary formations are complex and multilayered.

Borderline tumors show milder cytologic atypia and typically, no stromal invasion. These tumors may seed the peritoneum by tumors implants that are typically also noninvasive.

In general, malignant serous tumors spread to regional lymph nodes, including para-aortic lymph nodes, but distant lymphatic and hematogenous metastases are infrequent.

The prognosis for the clearly invasive serous cystadenocarcinoma is poor and depends heavily on the stage of the disease at the time of diagnosis. But it is much better for the borderline tumors even with the presence of peritoneal implants.

**B. Mucinous Tumors** differ from serous tumors essentially in the epithelium, which is of mucin-secreting cells similar to those of the endocervical or intestinal mucosa. These tumors occur in women in the same age range as those with serous tumors, but the majority are benign (80%), only 10% are malignant (cystadenocarcinomas), and 10% are of low malignant potential.

**Gross features** (Fig. 10-27)

The incidence of bilateral ovarian involvement is much lower than for their serous counterparts. Bilateral mucinous carcinomas of the ovary must be differentiated from metastatic adenocarcinomas of the gastrointestinal tract, which may present as ovarian masses (Krukenberg tumors).

Compared to their serous tumors, they show mucinous cystic contents and tend to be larger and multilocular but papillary formations are less common.

**Microscopic features** (Fig. 10-27).

Mucinous tumors are classified according to the type of the mucin-producing epithelial cells into endocervical, intestinal and müllerian-types. The intestinal type is almost always present in borderline mucinous tumors and mucinous carcinomas.

Unlike in their serous counterparts, psammoma bodies are not found.

Serosal penetration and solid areas point to malignancy.

Rupture of mucinous tumors may result in mucinous deposits in the peritoneum but typically do not result in the malignant growth referred to as *pseudomyxoma peritonei*. The vast majority if not all cases of the latter are caused by metastasis from the gastrointestinal tract, primarily the appendix. Metastasis of mucinous tumor of the gastrointestinal tract to the ovaries (*Krukenberg tumor*) may also mimic an ovarian primary tumor.

The prognosis of mucinous cystadenocarcinoma is somewhat better than that of the serous counterpart, but the stage rather than the histologic type is the major determinant of prognosis.

**C. Endometrioid Tumors** may be solid or cystic, but sometimes they develop as a mass projecting from the wall of an endometriotic cyst. They are distinguished by the formation of tubular glands (similar to those of the endometrium) within the linings of cystic spaces. Endometrioid tumors are usually malignant. They are bilateral in about 30% of cases, and up to 30% of women with these ovarian tumors have a concomitant endometrial carcinoma.

**D. Brenner Tumor** is an uncommon, solid, usually unilateral ovarian tumor consisting of an abundant stroma containing nests of transitional epithelium resembling that of the urinary tract. Although most are benign, both malignant and borderline tumors have been described.

**Germ Cell Tumors**
1. **Dysgerminoma**: these usually present within 10 to 30 years of age. Their microscopic picture is analogous to testicular seminoma. All are malignant but only 30% are aggressive and disseminate. All are radiosensitive with 80% cure.

2. **Yolk sac tumor & embryonal carcinoma** are similar to their testicular counterparts.

3. **Choriocarcinoma** presents within the first three decades of life. They are pathologically identical to placental choriocarcinoma.

4. **Teratomas** constitute up to 20% of ovarian tumors and arise in the first two decades of life; the younger the person, the greater the likelihood of malignancy. However, more than 90% of these germ-cell neoplasms are benign mature cystic teratomas.

**Benign (Mature) Cystic Teratomas** (Fig. 10-28) are characterized by differentiation of totipotential germ cells into mature tissues representing all three germ cell layers: ectoderm, endoderm, and mesoderm. Usually there is the formation of a cyst lined by recognizable epidermis stuffed with adnexal appendages—hence the common designation **dermoid cysts**. They rarely exceed 10 cm in diameter. On opening, they are often filled with sebaceous secretion and matted hair. Sometimes there is a nodular projection from which teeth protrude. Occasionally, foci of bone and cartilage, nests of bronchial or gastrointestinal epithelium, and other recognizable lines of development are also present. **Thyroid tissues are present in 10% of the cases.** These tumors are prone to undergo torsion (10% of cases), producing an acute surgical emergency.

**Immature Malignant Teratomas** differ from mature cystic teratoma by being often bulky, predominantly solid or near-solid, and punctuated by areas of necrosis. **Microscopically**, the distinguishing feature is a variety of **immature tissues** such as cartilage, bone, muscle, nerve, and other structures. Particularly worrying are foci of neuroepithelial differentiation, because most of these are aggressive and metastasize widely. (Fig. 10-29)

**Specialized Teratomas**

These include

1. **Struma ovarii**: composed entirely of mature thyroid tissue that may hyperfunction and produce hyperthyroidism.

2. **Ovarian carcinoid**, which in rare instances has produced the carcinoid syndrome.

**SEX CORD TUMORS** include

1. **Granulosa-thecal cell tumors**: mostly seen in postmenopausal but can occur at any age. They may be tiny or large, gray to yellow, with cystic spaces. They are composed of mixture of granulosa cells (in cords, sheets, or strands) and spindled, plump lipid-laden thecal cells. Granulosal elements may recapitulate ovarian follicle as **Call-Exner bodies** (small round cavity containing eosinophilic material and often shrunken nuclei). Nuclear folds or grooves (coffee-bean" appearance) is an important diagnostic feature (Fig. 10-30) **Hyperestrinism** occurs in 75% of cases; the effects depend on age: in children there is isosexual precocity; in adults & elderly there is abnormal uterine bleeding due to estrogen-induced endometrial hyperplasia. However, the tumor may be hormonally inactive or paradoxically androgenic The large amounts of estrogen (from thecal elements) may encourage the development of endometrial or breast carcinoma. Granulosal cell element may be malignant.

2. **Thecoma-fibroma group of tumors** occur at any age. Ovarian fibroma is solid gray and consists of spindle fibroblastic cells. Ovarian thecoma is yellow in color because they are composed of lipid-laden, plump thecal cells. Few tumors in this group elaborate estrogens. About 40%, for obscure reasons, produce ascites and hydrothorax (Meigs syndrome). They are rarely malignant.

3. **Sertoli-Leydig cell tumors** occur at any age. They are usually small and recapitulate the development of testis with tubules, or cords (Sertoli cells) and plump pink Leydig cells. Many of these tumors are functional (masculinizing or defeminizing). They are rarely malignant.

**METASTASES TO OVARY** are usually encountered in older ages. Mostly both ovaries are involved. **Grossly** there are solid gray-white masses as large as 20cm in diameter. Microscopically, there are malignant tumor cells arranged in cords or glands, and dispersed through a usually prominent fibroblastic background. Primaries include gastrointestinal tract, breast, and lung, & endometrium. When the infiltration is by mucin-containing signet ring cells the term **Krukenberg tumor** is applied. This is usually bilateral and nearly always of metastatic origin. (Fig. 10-31)
Clinical Correlations of ovarian cancers: all ovarian neoplasms produce no symptoms or signs until they are well advanced. Indeed, about a third of all ovarian neoplasms are discovered incidentally on routine gynecologic examination. The clinical presentation of all ovarian tumors is remarkably similar, except for the functioning neoplasms that have hormonal effects. When they become large enough they cause local pressure symptoms (e.g., pain, gastrointestinal complaints, and urinary frequency). Larger masses, notably the common epithelial tumors, may cause an increase in abdominal girth. Smaller masses, particularly dermoid cysts, sometimes become twisted on their pedicles (torsion), producing severe abdominal pain mimicking an "acute abdomen." Fibromas and malignant serous tumors often cause ascites, the latter resulting from metastatic seeding of the peritoneal cavity, so that tumor cells can be identified in the ascitic fluid. Among the many markers that have been explored, elevations of the protein CA-125 have been reported in 75% to 90% of women with epithelial ovarian cancer. However, as with carcinoembryonic antigen (CEA) in colon cancer, CA-125 measurements are of greatest value in monitoring response to therapy.

DISEASES OF PREGNANCY

Placental Inflammations and Infections

Infections reach the placenta either as an ascending infection through the birth canal (the most common) or through hematogenous route (transplacental infection).

Ascending infections are mostly bacterial and are complicated by premature rupture of the membranes that eventuates in premature birth. The chorioamnion shows neutrophilic infiltration with edema and congestion (acute chorioamnionitis). Extension of the infection may involve the umbilical cord and placental villi and cause acute vasculitis of the cord. In hematogenous spread of bacteria and other organisms the villi are most often affected (villitis).

Ectopic Pregnancy (Fig. 10-21) refers to implantation of the fertilized ovum in any site other than the normal uterine location. It occurs in 1% of pregnancies. In more than 90% it is a tubal pregnancy; other sites include the ovaries & abdominal cavity. Any factor that retards passage of the ovum along its course through the tube to the uterus predisposes to an ectopic pregnancy. In about half of the cases, such obstruction is a complication of chronic salpingitis, although intrauterine tumors & endometriosis may also impede passage of the ovum. In approximately 50% of tubal pregnancies, no anatomic cause can be demonstrated. Ectopic pregnancies are characterized by a normal early development of the embryo, with the formation of placental tissue, the amniotic sac, and decidual changes. With tubal pregnancies, however, the invading placenta eventually burrows through the wall, causing intratubal hematoma (hematosalpinx), intraperitoneal hemorrhage, or both. The tube is usually locally distended (up to 4 cm in diameter) by a contained mass of freshly clotted blood in which may be seen bits of gray placental tissue and fetal parts. The histologic diagnosis depends on the visualization of placental villi or, rarely, of the embryo. Until rupture occurs, an ectopic pregnancy may be indistinguishable from a normal one, with cessation of menstruation and elevation of serum and urinary placental hormones. Under the influence of these hormones, the endometrium (in 50% of cases) undergoes the characteristic hypersecretory and decidual changes. However, the absence of elevated gonadotropin levels does not exclude this diagnosis, because poor attachment with necrosis of the placenta is common. Rupture of an ectopic pregnancy may be catastrophic, with the sudden onset of intense abdominal pain and signs of an acute abdomen, often followed by shock. Prompt surgical intervention is necessary.

Gestational Trophoblastic Tumors

These are divided into four morphologic categories:
1. Hydatidiform mole
   a. Complete
   b. Incomplete
2. Invasive mole
3. Choriocarcinoma.
4. Placental site trophoblastic tumor
All the three produce human chorionic gonadotropin (hCG), which can be detected in the circulating blood and urine, at much higher titers than those found during normal pregnancy. The titers are progressively rising from hydatidiform mole to invasive mole to choriocarcinoma. In addition to aiding diagnosis, the fall or rise in the level of the hormone in the blood or urine can be used to monitor the effectiveness of treatment. Clinicians therefore prefer to lump the three conditions under the heading of gestational trophoblastic disease, because the response to therapy as judged by the hormone titers is more important than any arbitrary anatomic segregation of one lesion from another.

1. Hydatidiform Mole: Complete and Partial

The typical hydatidiform mole is a large mass of swollen chorionic villi, appearing grossly as grapelike structures. The swollen villi are covered by varying amounts of sometimes highly atypical chorionic epithelium. Two distinctive subtypes of moles have been characterized: complete and partial moles.

A. The complete hydatidiform mole does not permit embryogenesis and thus does not contain fetal parts. All of the chorionic villi are abnormal, and the chorionic epithelial cells are diploid (46, XX or, uncommonly, 46, XY).

B. The partial hydatidiform mole permits early embryogenesis and therefore contains fetal parts, has some normal chorionic villi, and is almost always triploid (e.g., 69, XXY).

The two patterns result from abnormal fertilization; in both two spermatozoa fertilize an ovum; in a complete mole an empty egg is fertilized, which yields a diploid karyotype composed of entirely paternal genes, while in a partial mole a normal egg is fertilized, resulting in a triploid karyotype with a preponderance of paternal genes.

For unknown reasons there is a much higher incidence of complete moles in Asian countries. Moles are most common before the age of 20 years and after the age 40 years, and a history of the condition increases the risk in subsequent pregnancies. Although traditionally discovered around week 12 of pregnancy because of a gestation that was "too large for dates," early monitoring of pregnancies by ultrasound has lowered the gestational age of detection, leading to the more frequent diagnosis of "early complete hydatidiform mole." In either instance, elevations of hCG in the maternal blood and absence of fetal parts or fetal heart sounds are typical.

**Gross features**
- In fully developed cases of complete moles the uterine cavity is filled with a delicate, friable mass of thin-walled, translucent cystic structures (Fig. 10-32).
- Fetal parts are rarely seen in complete moles but are common in partial moles. In the latter only some but not all of the villi are swollen. (Fig. 10-33)

**Microscopic features**

*The complete mole*
- There is hydropic swelling of all the chorionic villi, which are avascular.
- The central substance of the villi is a loose, edematous stroma.
- The chorionic epithelium almost always shows some degree of proliferation of both cytotrophoblast and syncytiotrophoblast (Fig. 10-32). The proliferation may be mild, but in many cases there is striking circumferential hyperplasia.

*Partial moles*
- The villous edematous swelling involves only some of the villi and the trophoblastic proliferation is focal and slight.
- The villi of partial moles have a characteristic irregular scalloped margin.
- In most cases of partial mole there is evidence of an embryo or fetus. This may be in the form of fetal red blood cells in placental villi or, in some cases, a fully formed fetus that, despite a triploid karyotype, is morphologically nearly normal in appearance. (Fig. 10-33)

Overall, 80% to 90% of moles do not recur after thorough curettage; 10% of complete moles are invasive, but not more than 2% give rise to choriocarcinoma. Partial moles rarely give rise to choriocarcinomas. With complete moles, monitoring the post-curettage blood and urinary hCG concentrations, particularly the more definitive β-subunit of the hormone, permits detection of incomplete removal or a more ominous complication.
and leads to the institution of appropriate therapy, including in some cases chemotherapy, which is almost always curative.

2. Invasive Mole (Fig. 10-34) is a complete mole that is more invasive locally but do not have the metastatic potential of a choriocarcinoma. An invasive mole retains hydropic villi, which penetrate the uterine wall deeply, possibly causing rupture and sometimes life-threatening hemorrhage. Local spread to the broad ligament and vagina may also occur. **Microscopically**, the epithelium of the villi is hyperplastic and atypical. **Metastases do not occur but hydropic villi may embolize to distant organs, such as lungs or brain.** However, these emboli are not metastatic and may regress spontaneously. Because of the greater depth of invasion into the myometrium, an invasive mole is difficult to remove completely by curettage, and therefore serum hCG may remain elevated. In most cases cure is possible through chemotherapy.

3. **Choriocarcinoma** is a very aggressive malignant tumor arises either from gestational chorionic epithelium or, less frequently, from totipotential cells within the gonads or elsewhere. They are much more common in Asian and African countries, reaching a frequency of 1 in 2000 pregnancies. The risk is somewhat greater before age 20 and is significantly elevated after age 40. Approximately 50% of choriocarcinomas complicate complete hydatidiform moles; about 25% arise after an abortion, and most of the remainder occur during what had been a normal pregnancy. Most cases are discovered by the appearance of a bloody or brownish discharge accompanied by a rising titer of hCG, particularly the β-subunit, in blood and urine, and the absence of marked uterine enlargement, such as would be anticipated with a mole. In general, the titers are much higher than those associated with a mole.

**Gross features** (Fig. 10-35)
- The tumor appears as very hemorrhagic, soft, nodular, necrotic masses within the uterus.
- Some times the primary lesion may self-destruct, and only the metastases tell the story.
- Very early, the tumor insinuates itself into the myometrium and into vessels.

**Microscopic features**
- Cytotrophoblastic cells tend to grow in clusters and sheets, separated by streaming masses of syncytiotrophoblast, forming the characteristic dimorphic growth pattern of mononucleate cytotrophoblast and syncytiotrophoblast.
- Hemorrhage and necrosis are usually present.
- In contrast to the case with hydatidiform moles and invasive moles, chorionic villi are not formed.

By the time most choriocarcinomas are discovered, there is usually widespread dissemination via the blood, most often to the lungs, vagina, brain, liver, and kidneys. Lymphatic invasion is uncommon. Despite the extreme aggressiveness of these neoplasms, which made them nearly uniformly fatal in the past, present-day chemotherapy has achieved nearly 100% cure. By contrast, there is relatively poor response to chemotherapy in choriocarcinomas that arise in the gonads (ovary or testis). This striking difference in prognosis may be related to the presence of paternal antigens on placental choriocarcinomas but not on gonadal lesions. Conceivably, a maternal immune response against the foreign (paternal) antigens helps by acting as an adjunct to chemotherapy.

4. **Placental Site Trophoblastic Tumor**
These uncommon tumors are diploid, often XX in karyotype, and are derived from the placental site intermediate trophoblast. They typically arise a few months after a pregnancy. Because intermediate trophoblasts do not produce hCG in large amounts, hCG concentrations are elevated, but only slightly. More typically these tumors produce human placental lactogen. These tumors are indolent and generally have a favorable outcome if confined to the endomyometrium. However, they are not as sensitive to chemotherapy as other trophoblastic tumors, and the prognosis is poor when spread has occurred beyond the uterus.

**Pre-eclampsia, Eclampsia (Toxemia Of Pregnancy)**
The syndrome of hypertension, proteinuria and edema developing in the third trimester of pregnancy, is referred to as **preeclampsia**. This occurs in 5% to 10% of pregnancies, chiefly with first pregnancies in women older...
than age 35 years. In those severely affected, convulsive seizures may appear, and the symptom complex is then termed eclampsia. Full-blown eclampsia may lead to disseminated intravascular coagulation (DIC), with all of its widespread ischemic organ injuries, and so eclampsia is potentially fatal.

Pathogenesis: a basic underlying feature in all cases is inadequate maternal blood flow to the placenta secondary to inadequate development of the spiral arteries of the uteroplacental bed. In the third trimester of normal pregnancy, the musculo-elastic walls of the spiral arteries are replaced by a fibrinous material, permitting them to dilate into wide vascular sinusoids. In preeclampsia and eclampsia, the musculoelastic walls are retained and the channels remain narrow. A decrease in vascular endothelial growth factor (VEGF) and an increase in antiangiogenic factors have been found to predate the onset of preeclampsia. While the exact basis of vascular abnormalities remains unknown, several consequences ensue:

1. Placental hypoperfusion with an increased predisposition to the development of infarcts
2. Reduced elaboration by the trophoblast of the vasodilators prostacyclin, prostaglandin E$_2$, and nitric oxide, which in normal pregnancies oppose the effects of renin-angiotensin-hence the hypertension of preeclampsia and eclampsia
3. Production by the ischemic placenta of thromboplastic substances such as tissue factor and thromboxane, which probably account for the development of DIC.

Pathologic features

A. Placental changes include:

1. Infarcts, which are a feature of normal pregnancy, are much more numerous. However, they may be absent.
2. Retroplacental hemorrhages occur in 15% of patients.
3. Premature aging of the villi may occur as evidenced by villous edema, hypovascularity, and increased production of syncytial epithelial knots.
4. Acute atherosis of spiral arterioles: prominent in well-advanced eclampsia & characterized by thickening and fibrinoid necrosis of the vessel wall with focal accumulations of lipid-containing macrophages. Necrosis of these cells releases lipid. Such lesions accentuate the placental ischemia.

B. Multiorgan changes may be present, reflecting the development of DIC. The kidneys are basically, shows changes consist of fibrin thrombi within the glomerular capillaries, accompanied by endothelial swelling. Focal glomerulitis may ensue. When numerous glomeruli are affected, blood flow to the cortex is reduced, possibly resulting in renal cortical necrosis that may be bilateral and fatal. Microvascular thrombi are also found in the brain, pituitary, heart, and elsewhere. They have the potential of producing focal ischemic lesions accompanied by microhemorrhages.

Preeclampsia appears insidiously in the 24th to 25th weeks of gestation, with the development of edema, proteinuria, and rising blood pressure. Should the condition evolve into eclampsia, renal function is impaired, the blood pressure mounts, and convulsions may occur. Prompt therapy early in the course aborts the organ changes, with clearance of all abnormalities promptly after delivery or cesarean section.