Chapter 13
The Breast and Female Reproductive System

Learning Objectives

- Describe normal structure and physiology of breast and common developmental abnormalities
- Explain applications and limitations of mammography in the diagnosis and treatment of breast disease
- Describe three common breast diseases that present as lump in the breast
- Describe clinical manifestations of breast carcinoma, methods of diagnosis and treatment
- Explain role of heredity in the pathogenesis of breast carcinoma

Learning Objectives

- Describe common genital tract infections and relate these to sexually transmitted diseases
- Describe clinical manifestations and complications of endometriosis
- List common causes of irregular uterine bleeding
- Describe common diseases of the cervix, endometrium, myometrium, and vulva

Breast Structure (1 of 4)

- Breasts: modified sweat glands specialized to secrete milk
- Main function is milk production
- Two main types of tissues:
  - Glandular tissues (lobules and ducts)
  - Stromal (supporting) tissues
  - Supporting tissue includes fatty and fibrous connective tissue that give the breast its size, shape, and support
- Two main types of breast changes:
  - Benign (non-cancerous)
  - Malignant (cancerous)

Breast Structure (2 of 4)

- Composed of 20 lobes of glandular tissue:
  - Each lobe made up of a cluster of milk-producing glands or lobules
  - Lobules connected by branching ducts or small tubes and converge to the nipple
  - Fat and connective tissue, blood vessels, lymph vessels
- Suspensory ligaments: bands of fibrous tissue extending from skin of breast to the connective tissue covering chest wall muscles
Breast Structure (3 of 4)

- Abundant blood supply and lymphatic drainage
  - Lymph vessels carry lymph fluid instead of blood
  - Most lymph vessels of breast lead to the axillary nodes (supraclavicular and mediastinal nodes)
  - If breast cancer cells reach axillary nodes and continue to grow, nodes swell and cancer more likely to spread to other organs

Breast Structure (4 of 4)

- Puberty: enlarge in response to estrogen and progesterone
- Post-pubertal changes
  - Proliferation of glandular and fibrous tissue
  - Accumulation of adipose tissue
- Variations in breast size depend on amount of fat and fibrous tissue rather than glandular tissue
- Extremely responsive to hormonal stimulation
  - Menstrual cycle: cyclic hyperplasia followed by involution
  - Pregnancy and lactation: hypertrophic glandular and ductal tissues
  - After menopause: sex hormone levels decline, breasts gradually decrease in size

Tissue Changes Secondary to Hormone Levels

Breast Examination

- Mammogram may identify lesions not detected on clinical examination
  - Denser cysts and tumors: white on mammogram
  - Less dense fatty tissue: dark on mammogram
  - Cysts and benign tumors: well circumscribed
  - Malignant tumors
    - Have irregular borders
    - Frequently contain fine flecks of calcium

Mammogram

- Fatty tissue: appear dark
- Fibrous and glandular tissue: appear as white strands

Calcifications

- Stippled calcification in tumor
- Ductal carcinoma, with necrosis and calcification
Abnormalities in Breast Development
(1 of 3)

• Embryologically, breasts develop from column of cells (mammary ridges) located anteriorly from axilla to upper thighs
• Most of the ridges disappear during prenatal development except for those at the midthoracic area, giving rise to breasts and nipples

Abnormalities in Breast Development
(2 of 3)

• Accessory breasts and nipples: most commonly found in the armpits or on lower chest below and medial to the normal breasts
• Unequal development: fully developed breasts are usually similar in size but not identical, sometimes one fails to develop as much as its counterpart

Abnormalities in Breast Development
(3 of 3)

• Breast hypertrophy: at puberty, one or both breasts over-respond to hormonal stimulation; true hypertrophy is from overgrowth of fibrous tissue, not glands or fat
• Gynecomastia: ductal and fibrous tissue of adolescent male breast proliferate affecting one or more breast; from temporary imbalance of female and male hormones (increase in estrogen) in the male at puberty

Benign Cystic Change in the Breast

• Very common benign condition; also called fibrocystic disease
• Focal areas of proliferation of glandular and fibrous tissue
• Irregular cyclic response to hormones during menstrual cycle
• Ultrasound examination helpful in distinguishing a cystic from a solid mass
• Treatment
  – Aspiration of cyst
  – Surgical excision if no aspiration

Common sites of accessory breasts

Extra nipple below and medial to left breast and nipple

Benign breast cysts, in cross-section, previously filled with fluid

Ultrasound, breast cyst
Fibroadenoma

- Benign
- Well-circumscribed tumor of fibrous and glandular tissue
- Common in young women
- Surgically excised

Breast Carcinoma

- Risk factors
  - Familial tendency (mother or sister with breast cancer)
  - Hormonal factors
  - Birth of first child after age 30
  - Early menarche
  - Late menopause
  - Occurs in both sexes, but rare in men, whose breasts are not subject to stimulation by ovarian hormones
  - Occurs in 1 in every 10 women

Breast Carcinoma

- Hormones have been used for many years to treat menopausal symptoms consisting of estrogen alone or estrogen + progestin
  - Progestin: synthetic compound with progesterone activity
- Combined hormone therapy (estrogen-progestin) increases density of breast tissue, complicating the interpretation of mammograms
- Risk related to hormone treatment
  - Long-term estrogen-progestin use significantly increases risk of breast carcinoma (8%)
  - Long-term use of estrogen without progestin slightly increases risk of breast carcinoma (1%)

Breast Carcinoma

- Inheritance of mutant breast cancer susceptibility genes
- Mutant BRCA1 gene
  - Increases breast and ovarian carcinoma risk
  - Breast cancer risk at 80%
  - Ovarian cancer risk at 20–40%
  - Large gene with many different mutations
- Mutant BRCA2 gene
  - Breast cancer risk at 80%
  - Lower ovarian carcinoma risk at 10–20%

Breast Carcinoma (4 of 4)

- Clinical Manifestations
  - Lump in the breast
  - Nipple or skin retraction
  - Skin edema (orange peel sign)

- Tumor infiltrates breast and becomes fixed to chest wall; metastasis

Classification of Breast Carcinoma

- Site of origin
  - Ductal carcinoma (90%)
  - Lobular carcinomas (10%)
  - Non-infiltrating or in situ cancer
    - Confined initially within the duct or lobule
    - Becomes invasive and extends toward adjacent breast tissue
- Presence or absence of invasion
- Degree of differentiation of tumor cells
  - Well-differentiated: cells that resemble normal breast tissue
  - Poorly-differentiated: bizarre cells arranged haphazardly, immature; very different from normal breast tissue
Evolution of Breast Carcinoma
• Early stages: too small to be detected by breast exam
  – Mammogram can identify carcinoma up to 2 years before detection by breast exam
• Cancer continues to grow, initially in situ; eventually becomes invasive
• Metastasizes to axillary lymph nodes and distant sites
• Problems with late metastases
• Early diagnosis allows prompt treatment and improves the cure rate

Breast Carcinoma Treatment: Surgical Resection
• Modified radical mastectomy
  – Also called total mastectomy with axillary lymph node dissection
  – Resecting entire breast, axillary tissue with lymph nodes; leaves pectoral muscles
  – May be followed by breast reconstruction
• Partial mastectomy: removing only part of breast with the tumor
  – Lumpectomy: removing tumor and small amount of adjacent breast tissue
  – Axillary lymph nodes removed in both lumpectomy and partial mastectomy followed by radiation to eradicate any remaining carcinoma in the breast

Breast Carcinoma Treatment: Adjuvant Therapy
• To eradicate any tumor cells that may have spread beyond the breast
  – Anticancer drugs (adjuvant chemotherapy)
  – Anti-estrogen drugs (adjuvant hormonal therapy)
• Whichever method of treatment is selected, part of tumor obtained is surgically tested to:
  – Detect presence of estrogen and progesterone receptors
  – Detect amplification of HER-2 gene that speeds growth rate of tumor cells; HER-2 positive tumors have less favorable prognosis

Determining Hormone Receptor Status of Tumor
• Prognosis
  – Estrogen receptors (ER) and progesterone receptors (PR) in breast carcinoma
  – Hormone receptor positive tumors are better differentiated with favorable prognosis
  – Patients with ER positive tumors may receive adjuvant hormonal therapy with antiestrogen drug
• Guide for treatment: tumors with hormone receptors respond to anti-estrogen adjuvant therapy

Recurrent and Metastatic Carcinoma (1 of 2)
• May appear many years after original tumor has been resected
• Tumor no longer curable, treatment is to control growth, relieve symptoms, and improve quality of life
• Methods of treatment depend on the following factors:
  – Hormone receptor status of tumor
  – Age of patient
  – Length that elapsed from initial treatment to appearance of metastasis
  – Pre- and postmenopausal, hormone-receptor positive tumor: use anti-estrogen drugs
Recurrent and Metastatic Carcinoma (2 of 2)

- Methods of treatment
- Hormone-receptor positive tumor
  - Premenopausal: anti-estrogen drugs
  - Postmenopausal: aromatase inhibitor drugs
- Hormone-receptor negative tumor
  - Hormonal manipulation if unresponsive to tamoxifen or aromatase inhibitor
- Radiation
  - To control metastatic deposits in bone and soft tissues

A Lump in the Breast

- Diagnostic possibilities
  - Cystic disease
  - Fibroadenoma
  - Carcinoma
- Diagnostic approach
  - Clinical evaluation
  - Mammogram
  - Biopsy

Discussion

- Which statement regarding breast cancer risk is UNTRUE?
  A. Late menses and early menopause can increase breast cancer risk
  B. Risk is higher in families with a history of breast cancer
  C. Hormone use can increase the risk of breast cancer
  D. The risk is higher for women who have never borne children

Female Genital Tract: Infections (1 of 3)

- Vaginitis: common, causes vaginal discharge, itching, and irritation
  - Candida albicans
  - Trichomonas vaginalis
  - Gardnerella (Hemophilus) vaginalis in conjunction with anaerobic bacteria (nonspecific vaginitis)
- Cervicitis: mild chronic inflammation; common in women who have had children
  - More severe inflammation caused by gonococci or Chlamydia
  - May spread to infect tubes and adjacent tissues (PID)

Female Genital Tract: Infections (2 of 3)

- Salpingitis: tubal infection
- Pelvic inflammatory disease, PID: inflammation of fallopian tubes, along with ovaries at times
- Manifestations and complications
  - Lower abdominal pain and tenderness, fever, leukocytosis
  - Usually secondary to ascending spread of cervical gonorrheal or Chlamydia infection
  - Tubal scarring following healing predisposes to ectopic pregnancy or may cause sterility

Female Genital Tract: Infections (3 of 3)

- Condylomas: venereal warts in genital tract
  - Benign tumor-like overgrowths of squamous epithelium
  - Acquired and transmitted by sexual contact
- Common locations
  - Mucosa of cervix and vagina
  - Around vaginal opening
  - Around anus
- Treatment: to destroy lesions
  - Applying a strong chemical
  - Electrocoagulation
  - Freezing
  - Surgical excision
Chronic pelvic inflammatory disease, swollen tubes with occluded fimbriated ends

Multiple condylomas in cervical and vaginal mucosa

Endometriosis (1 of 2)
- Deposits of endometrial tissue outside normal location in endometrial cavity
  - Ectopic sites: uterine wall; ovary; elsewhere in pelvis, appendix, rectum
  - Ectopic endometrium responds to hormonal stimuli and undergoes cyclic menstrual desquamation and regeneration
  - Secondary scarring may obstruct fallopian tubes
- Diagnosis: laparoscopy
  - Allows visualization of ectopic deposits followed by removing or destroying these deposits surgically, through drugs, or hormones

Endometriosis (2 of 2)
- Treatment
  - Synthetic hormones with progesterone activity to completely suppress menstrual cycle
  - Oral contraceptives to suppress ovulation: makes endometrium thin and atrophic and menstrual cycles light, which retards progressing of endometriosis and associated scarring
  - Drugs that suppress output of gonadotropin from pituitary gland: leads to decline in ovarian function, allowing deposits of endometriosis to regress by being deprived of cyclic estrogen-progesterone stimulation

Endometriosis, cystic deposit of endometriosis filled with old blood in uterine wall

Cervical Polyps
- Cervical polyps
  - Benign, arise from the cervix
  - Usually small but may be quite large
  - Erosion of tip may cause bleeding
  - Surgical removal
- Cervical dysplasia: abnormal growth and maturation of cervical squamous epithelium
- Dysplastic changes range from:
  - Mild dysplasia
    - Result of cervical inflammation
    - Regresses spontaneously
  - Severe dysplasia
    - Does not regress
    - May progress to in situ carcinoma
    - May progress to invasive carcinoma

Large cervical polyp
Cervical Intraepithelial Neoplasia

(1 of 2)

- Cervical dysplasia and in situ carcinoma considered very closely related.
- Constitute different stages in a progressive spectrum of epithelial abnormalities classified as cervical intra-epithelial neoplasia, CIN:
  - Grade I: Mild dysplasia
  - Grade II: Moderate dysplasia
  - Grade III: Severe dysplasia
- Some human papilloma virus (HPV) strains that cause cervical condylomas are carcinogenic and predispose to cervical neoplasia.

Cervical Intraepithelial Neoplasia

(2 of 2)

- HPV genital tract infections are common:
  - More than 80 different strains of HPV
  - 40 types can infect genital tract
  - 8 strains are high-risk types and considered carcinogenic
  - Common in young sexually active women
  - > 90% infections resolve spontaneously in 6-12 months
  - Some may have repeated infections
- Diagnosis: HPV test to supplement Pap smear when cytologic changes in Pap smear are inconclusive (atypical squamous cells of undetermined significance).
  - If HPV test is negative, cytologic changes are not significant.

Cervical epithelial dysplasia

caused by papilloma virus

Dysplastic epithelial cell identified in
Papanicolaou smear

Cervical Dysplasia and Carcinoma

(1 of 2)

- Squamocolumnar junction or transition zone
- Cervical abnormalities develop first in cells at the junction between squamous epithelium at exterior of the cervix and the columnar epithelium lining cervical canal
- Usually located at the external os
- Pap smear shows abnormal cells
- Colposcopy localizes abnormalities
- Biopsies establish diagnosis

Cervical Dysplasia and Carcinoma

(2 of 2)

- Treatment depends on extent of disease
- Dysplasia and in situ carcinoma:
  - Cryocautery (freezing)
  - Surgical excision of abnormal area
  - Hysterectomy (removal of uterus)
  - Results are excellent
- Invasive carcinoma:
  - Radiation
  - Radical hysterectomy (resection of uterus, fallopian tubes, ovaries, adjacent tissues)
  - Results are less satisfactory.
### Endometrial Disorders

- Benign endometrial hyperplasia
  - Associated with irregular uterine bleeding
- Benign endometrial polyps
  - Common
  - May bleed if tip is eroded
- Endometrial adenocarcinoma
  - Related to prolonged endometrial stimulation by estrogen use
  - Irregular uterine bleeding or postmenopausal bleeding

### Uterine Myomas

- Benign smooth muscle tumors from uterine wall
  - Approximately 30% of women over 30 years of age have myomas
  - May cause irregular/heavy uterine bleeding
  - Symptoms related to pressure on bladder and rectum

### Irregular Uterine Bleeding

- Dysfunctional uterine bleeding:
  - Occurs because follicle fails to mature and no corpus luteum is formed (anovulatory cycle)
  - Disturbance of normal cyclic interaction of estrogen and progesterone on the endometrium
  - Uterus is subjected to continuous estrogen stimulation and responds by shedding and bleeding in an irregular manner instead of shedding all at once as in a normal period (anovulatory bleeding)
- Other causes of uterine bleeding
  - Benign endometrial hyperplasia
  - Endometrial and cervical polyps
  - Uterine myomas
  - Uterine carcinoma

### Normal Cycle

- First half: endometrial glands and stroma proliferate under influence of estrogen from ovarian follicle
- Midcycle: ovulation occurs
  - Follicle discharges its egg, becomes a corpus luteum that produces estrogen and progesterone
  - Progesterone: endometrium undergoes secretory phase to prepare for receiving fertilized ovum
- If no pregnancy occurs
  - Corpus luteum degrades
  - Estrogen-progesterone levels fall
  - Secretory endometrium is shed with blood
- New cycle begins

### Dysmenorrhea (1 of 2)

- Primary dysmenorrhea
  - Most common type; pelvic organs are normal
  - Menstrual periods are painless for first two years after menarche because the cycles are anovulatory
  - Dysmenorrhea occurs when regular ovulatory menstrual cycles begin
  - Prostaglandins synthesized under the influence of progesterone during secretory phase of cycle and released from endometrium during menses and stimulate myometrial contractions causing pain
**Dysmenorrhea (2 of 2)**

- Primary dysmenorrhea
  - Crampy lower abdominal pain that begins just before menstruation
  - Pain lasts for 1-2 days after onset of menstrual flow
  - Treatment: prostaglandin inhibitors, oral contraceptives
- Secondary dysmenorrhea: from various diseases of the pelvic organs, such as endometriosis
  - Treatment: correct underlying cause

**Ovarian Cysts (1 of 2)**

- Ovarian cysts
  - Arise from ovarian follicles or corpora lutea that have failed to regress normally and converted to fluid-filled cysts
- Functional cysts
  - Follicle and corpus luteum cysts from deranged maturation and involution, regress spontaneously, do not become large
- Endometrial cysts
  - Endometrial deposits in ovary filled with old blood and debris

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**Ovarian Cysts (2 of 2)**

- Benign cystic teratoma (dermoid cyst)
  - Arise from unfertilized ova that undergo neoplastic change
  - Contains skin, hair, teeth, bone, parts of gastrointestinal tract, thyroid, and other tissues growing in a jumbled fashion
- Malignant teratoma
  - Very rare

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**Section of normal ovary**

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**Ovarian Tumors (1 of 2)**

- Resemble epithelium found in other parts of the genital tract
- Serous tumor: resembles cells lining fallopian tubes
  - Cystadenoma: benign, cystic serous tumor
  - Cystadenocarcinoma: neoplastic epithelium may extend on the surface of tumor and break off, implanting in other parts: pelvis, peritoneal cavity, omentum
- Mucinous tumor: resembles mucus-secreting tumor of endocervix
  - Mucinous cystadenoma
  - Mucinous cystadenocarcinoma
Ovarian Tumors (2 of 2)

- Endometrioid tumor: resembles endometrial tissue
  - Endometrioid carcinoma
- Fibroma: from fibrous connective tissue cells of ovary
- Granulosa-theca cell tumor
  - Ovarian tumor that produces estrogen
  - Arises from the granulosa cells or estrogen-producing cells that line the follicle or from theca cells located adjacent to follicle cells
  - Induces excessive endometrial stimulation from estrogen produced by tumor
- Male hormone-producing ovarian tumors
  - Induces masculinization

Diseases of the Vulva

- Vulvar dystrophy
  - Irregular white patches on vulvar skin (leukoplakia)
  - Intense itching
  - May progress to carcinoma
  - Local treatment usually effective
- Carcinoma of the vulva
  - Found in pre- and post-menopausal women
  - Usually with a preexisting vulvar dystrophy
  - Treated by vulvectomy and excision of inguinal lymph nodes

Toxic Shock Syndrome (TSS) (1 of 2)

- Occurs most commonly in women using high-absorbency tampons
- No tampon can be considered entirely free from risk
- Caused by toxin produced by Staphylococci in vagina
- Menstrual blood and secretions serve as good culture medium for bacteria
- Tampons slow drainage of menstruate, may cause superficial erosions on vaginal mucosa allowing absorption of toxin through injured skin

Toxic Shock Syndrome (TSS) (2 of 2)

- Clinical manifestations
  - Fever, vomiting, diarrhea, muscle aches and pains
  - Erythematous or sunburn-like rash followed by flaking and peeling
- Treatment
  - General supportive measures until effects of toxin wear off
  - Discontinue tampon use; TSS recurrence rate is 30%
  - Antibiotics to eradicate Staphylococci do not shorten course of disease
  - TSS also occurs from staphylococcal infections of skin, bones, kidneys, with toxin released in the bloodstream

Contraception

- Natural family planning
  - Avoidance of intercourse at time of ovulation
- Artificial contraception
  - Barrier methods: diaphragms and condoms; effective, no side effects
  - Oral contraceptives: suppress ovulation
    - Side effects: increased tendency for thromboembolic complications, especially among smokers; hypertension
  - Intrauterine contraceptive devices, IUDs: prevent implantation
    - Increased incidence of tubal infections and tubal pregnancies
Emergency Contraception

- Prevents pregnancy following unprotected intercourse or sexual assault
  - Sperm can survive as long as 6 days in genital tract and can still fertilize an ovum
  - Intercourse several days before ovulation can lead to a pregnancy
  - Single progestin pill (1.5 mg, Levonorgestrel)
  - Prevents pregnancy by interfering with ovulation, tubal transport of ovum, and implantation within endometrium
- Effectiveness
  - If taken within 12 hours after intercourse, risk of pregnancy <1% and 3% if taken within 72 hours
  - Some protection is still provided for as long as 5 days

Discussion

- A 23-year-old female presents with high fever, chills, vomiting, and muscle aches. On examination, patient has a markedly low blood pressure with a rash on her trunk. Search for possible sites of infection pointed to the vaginal area and tampon use. Patient is on the fifth day of her monthly period.
  A. Vaginitis
  B. Cellulitis
  C. Drug reactions
  D. Vulvar carcinoma
  E. Toxic Shock Syndrome