TEXTBOOK OF GYNECOLOGY

Mina Garashova

Elmira Aliyeva

Introduction:

This textbook was written by the members of the Obstetrics and Gynecology Faculty I at the Azerbaijan Medical University as a study aid to help students and resident physicians to obtain the knowledge needed for careful and effective practice. It is enable rapid assimilation of key information that reflects modern clinical needs.

This textbook based on general information about the anatomy and physiology of female reproductive organs, essentials of gynecological diseases and knowledge and experience of leading foreign and Azeri scientists.

Gynecology is a branch of medicine that deals with the diseases and routine physical care of the reproductive system of women. It is all about the diseases, methodical approach to them, prevention, cure.

We hope that from our book you will get a lot of useful information that will be helpful in your future medical practice.

List of Abbreviations

ACTH-Adrenocorticotropic hormone

ASCUS-atypical squamous cells of undetermined significance

BV-bacterial vaginosis

BMI-body mass index

BRCA1, 2-breast cancer antigen

CA 125-cancer antigen

CIN-cervical intraepithelial neoplasia

CRH-Corticotropin-releasing hormone

CT-computed tomography

D&C-dilatation and curettage

DHEA-S-Dehydroepiandrosterone sulfate

DNA-deoxyribonucleic acid

E3-Estriol

FSH-Follicle-stimulating hormone

GH-Growth hormone

GnRH-Gonadotropin-releasing hormone

hCG-Human chorionic gonadotropin

HIV-Human immunodeficiency virus

HPV-Human papillomavirus

HGS-Hysterosalpingography

ICSI-intracytoplasmic sperm injection

IUD-intrauterine device

IUFD-intrauterine fetal demise

IVF-In vitro fertilization

LH-Luteinizing hormone

MRI-magnetic resonance imaging

MRKH-Mayer-Rokitansky-Kuster-Hauser syndrome

MURCS-Mullerian duct aplasia-renal agenesis-cervicothoracic somite dysplasia

OC-oral contraceptives

PCOS-polycystic ovary syndrome

PCR-polymerase chain reaction

PID-pelvic inflammatory disease

PMDD-premenstrual dysphoric disorder

PMS-premenstrual syndrome

POP-pelvic organ prolapse

PRL-Prolactin

RMI-risk for malignancy index

STIs-sexually transmitted infections

TSH-Thyroid-stimulating hormone

US-ultrasonography

VVC-vulvovaginal candidiasis

Contents

Chapter 1 Clinical Approach to the Patient

Gynecological History Taking

A careful history and physical examination should form the basis for patient evaluation and clinical management in gynecology. This chapter reflects the essential details of the clinical approach to, and evaluation of gynecological patient.

History includes:

>Identifying history

>Chief complaints, history of present illness

>Past medical and surgical history

>Medications, allergies, personal habits, working-living conditions

>Family history

>Menstrual history

>Obstetrical history, contraceptive history

>Sexual history

>Menopausal history in woman >40

Identifying History

This history includes personal information of the patient: name, age, residence-rural/urban, contact number, address, marital status, educational background, occupation.

The incidence of gynecological diseases varies in age categories: in childhood foreign body vulvo-vaginitis, intravaginal and ovarian tumors are more common. Adolescents mostly have such problems as delayed puberty, menstrual disorders,

PCOS, uterovaginal abnormalities. Women in reproductive age are faced with such gynecological problems as menstrual irregularities, fibroids, endometriosis, STI, pregnancy related problems. Older age women have menopause-related problems, malignancies.

Certain gynecological problems, like STI, Endometriosis, PCOS, ovarian tumors are more common in urban dwellers. Rural citizens are more likely to have problems due to multiparity-genital prolapse and late stages of malignancies.

Education and occupation status give us information about the socio-economical status of the patient.

Marital status: married, unmarried, separated, women in relationship.

Chief Complaints, History of Present Illness

The patient is asked to state her main complaint. Complaints should be noted in chronological order and with patient priorities .It is important to ask about the duration, exact timing of onset, and the severity of the problem.

Common presenting problems are:

Abnormal vaginal bleeding

Vaginal bleeding before the age 9 and after the age 52 years, also prolongation of the menses beyond 7 days, or bleeding between menses are causes for concern and require investigation.

Amenorrhea

Amenorrhea is divided to primary or secondary. Most common causes of amenorrhea are pregnancy, menopause, hormonal changes, and congenital abnormalities of genital tract. There are symptoms of premature ovarian failure.

Abdominal pain

The majority of gynecological problems are associated with abdominal pain. Character of pain may be different: dull, heaviness, spasmoidic, twisting. The pain may be acute or chronic.

Most common gynecologic causes are salpingo-oophoritis with peritoneal inflammation, torsion and infarction of the ovarian cyst, endometriosis, and rupture of ectopic pregnancy, benign and malignant pelvic tumors.

Dysmenorrhea

It is associated with dull pain in the lower abdomen, accompanied by headache, dizziness, nausea, vomiting, fluid retention, drop in perfomance and mood. It is related to the menstrual cycle.

Vaginal Discharge

Generally it is characteristic symptom of the vulvovaginitis and STI. Vaginal discharge may be mucous, watery, bloody, purulent, curd like thick discharge, and usually is associated with itching, burning, blood staining, and fishy odor.

Other symptoms

Other symptoms include dyspareunia, inabilty to conceive, urinary symptoms, dischezia, constipation, genital swelling, uterine prolapse, weight gain/weight loss.

Past Medical and Surgical History

It's very important to ask detailed medical history. In addition to common disorders, such as diabetes mellitus, obesity, thyroid disorder that affect gynecological problems (irregularity of menstrual cycle, infertility, PCOS, development of benign and malignant tumors) all the serious medical conditions should be recorded. For example, asthma, chronic lung disease, constipation increase intraabdominal pressure, and predispose to develop uterine prolapse, coagulation disorders present with dysfunctional uterine bleeding.

Childhood diseases, rickets, psychological problems

Previous abdominal/pelvic surgery may cause chronic abdominal pain and infertility as a result of adhesions. Each surgical procedure should be recorded, including date, hospital and complications.

Family History

A number of gynecological diseases have familial predispositions. Breast, ovarian, endometrial cancer syndrome occurs in women having BRCA mutation carriers in family. Women with family background of diabetes, hypertension, and obesity are prone to ovarian and endometrial cancer and need careful evaluation in peri- and postmenopausal period.

Medications, Allergies, Personal Habits, Occupational Conditions

A list of current medications is important. They are medications for: diabetes, hypertension, hormone replacement therapy, NSAID, corticosteroids, psychotropic drugs, contraceptives, using of vaginal pessary.

Presence of allergic reactions to any medications or other elements should be recorded.

Personal habits: smoking, alcohol (since, how long and amount), addiction to cocaine, marijuana, sleeping pills.

Women exposed to radiatons, solvents, insulators, insecticides in the workplace are prone to develop cancer, fetal malformations, and spontaneous abortions.

Menstrual History

The menstrual history should include the age at menarche (average 12-13 years), characteristics of the menstrual cycle like duration of bleeding (average is 3-7

days) interval between periods (21-35 days), regularity, volume, character of the flow (scant, normal, heavy), premenstrual symptoms, painless, painful.

Obstetric History, Contraceptive History

Parity, outcomes, number of miscarriages, abortions, IUFD, neonatal death, molar and ectopic pregnancies, history of postnatal septical processes, that may cause PID, infertility, pelvic pain, miscarriage.

Each pregnancy and delivery, and associated complications should be listed sequentially with relevant details and dates.

The type and duration of each contraceptive method must be recorded along with their complications, such as amenorrhea, abnormal uterine bleeding, galactorrhea, thromboembolic disease as a result of prolong use of combined OC, dysmenorrhea, and pelvic infections with untrauterine device, failure of contraception with the diaphragm, contraceptive sponge or vaginal creams and tablets. Using of barrier contraceptives decreases incidence of STI and cervical cancer.

Sexual History

Sexual history should be collected very careful .Patient may feel embarrassed in this task. Gynecologist must have earned her confidence and faith. The information about the onset of sexual life, partner, number of partners, current relationship, frequency of sexual contacts, dyspareunia, lack of orgasm, vaginismus, vaginal dryness, disuria associated with sexual intercourse should be discussed tactfully.

Menopausal History

It is useful to know age of onset of menopause, any preceding symptoms like sweating, hot flashes, and dryness of vagina, abnormal uterine bleeding, decreasing sex desire, sleep disturbances, obesity, and incontinence of urine.

If women receive replacement hormonal therapy, daily Calsium supplements. Family history of diabetes, breast, uterine and ovarian cancer, and osteoporosis should be obtained.

Physical Examination

Clinical examination is essential and integral part of clinical approach to the patient .A complete physical examination should be performed on each patient and repeated annually .The initial examination should include the patients:

>weight/ hight- BMI calculating

>vital signs (temperature, pulse rate, respiratory rate, blood pressure)

>general appearance-the patients body built ,posture, state of nutrition, coloration of the skin and mucous(pale ,cyanotic, icteric),the development of subcutaneous fat ,hair growth ,demeanor.

>development of secondary sexual characteristics by Tanner scale (table 1-1)

Tanner stage	FEMALES	
	Breasts	Pubic hair
1	Nipple elevation only	None
2	Small raised breast bud	Growth along labia, sparse, lightly pigmented
3	Breast and areola enlarge with no contour difference	Increases in amount, darkens, starts to curl
4	Further enlargement with areola and nipple projecting to form secondary mound	Resembles adult type, but not spread to medial thighs
5	Adult contour with areola and breast in same contour, nipple protruding	Spreads to medial thighs, adult distribution

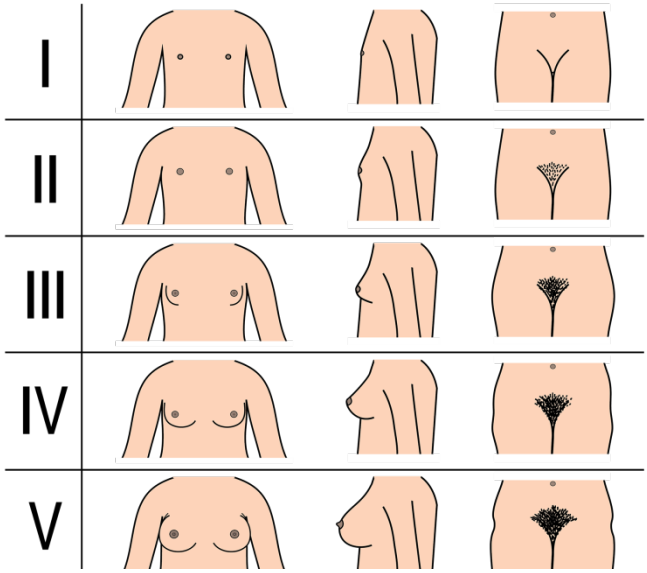


Table 1-1 The Tanner scoring system for secondary sexual characteristics

>breast development (picture 1- 4 stages of breast development), clinical breast examination:

>axilla-hair growth, lymph nodes

>face and body hair growth-hirsutism, evaluation by Feriman-Gallway scale (Figure 1-1)

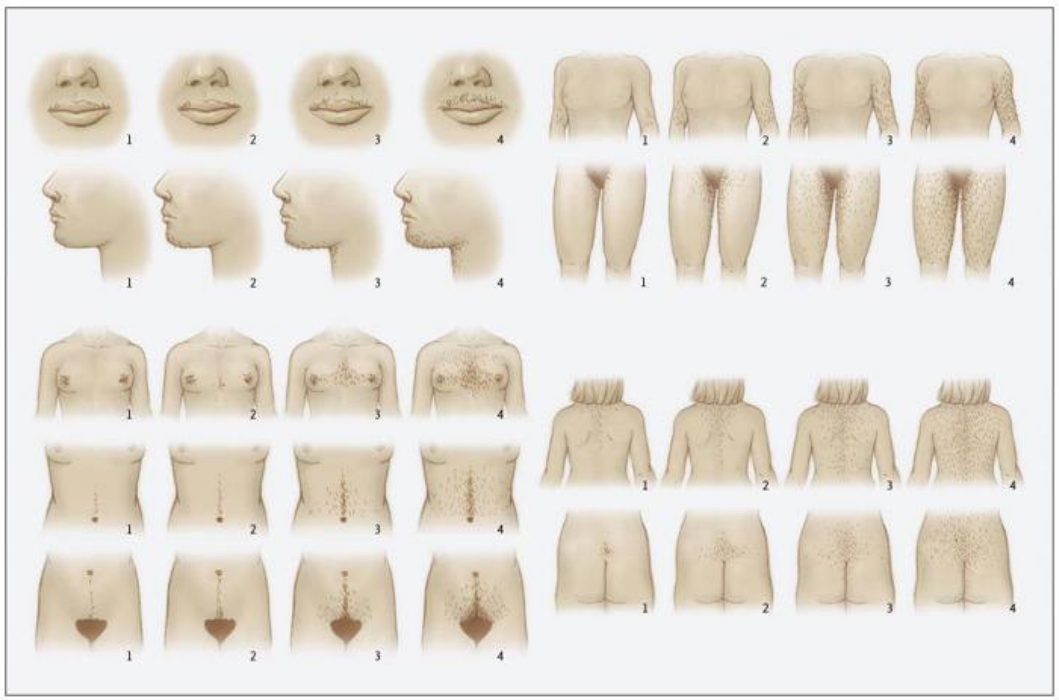


Figure 1-2 The Ferriman-Gallwey scoring system for hirsutism

>examination of the abdomen .It is critical in the evaluation of the gynecologic patient. It is include

>inspection (color of skin, pigmentation, presence and distribution of hair, striae and operative scars; prominent veins, caput medusa, umbilical slitting, hernia sites

>palpation: It is important to palpate any abdominal mass.The characteristics of the mass, such as size, whether it is cystic or solid, smooth or nodular, fixed or mobile, assosiated with ascites, or not should be noted.

>percussion

Pelvic Examination

Examination of external genitalia

Examination is usually performed in dorsal position with hip and knee flexed and feet resting on the examination couch .It must be conducted systematicaly and with careful sensitivity.

Vulva

Development of the labia, the character of the hymen and vaginal introitus, the character and distribution of hair, presence of any clitoromegaly, cysts, tumors or Bartholin's gland inflammation should be noted.

Speculum examination

Examination is performed with bivalve speculum (Figure 1-2), which should be warmed and lubricated .The main characteristics of the vagina: color, dryness, folding of the vaginal wall, mucosal lesions, cysts, growth, bleeding from vaginal mucosa, structural anomalies.

Figure 1-2 Bivalve vaginal speculum

The cervix should be inspected to determine its size, shape (conical, bulbous), color, external os (centrally placed or transverse configuration), presence of tears lacerations, ectropion, erosion, squamo-columnar junction, transformation zone, discharge, Nebotian follicles, bleeding.

Bimanual Examination

The bimanual examination provides information about the uterus and adnexa. The bladder should be emptied, gloved lubricated index and middle fingers are inserted into the vagina .Once terminal finger reaches the cervix it's palpated for consistency, contour, size, tenderness and motion.

The uterus is evaluated by placing the abdominal hand flat over the supra pubic lower abdomen with the fingers pressing above the symphysis pubis. After vaginal fingers put in the posterior fornix, uterus is pushed upward and anteriorly towards the abdominal hand. As the uterus is felt between the examining fingers of hands, the size, configuration, consistency, mobility of the organ are appreciated.

By shifting the abdominal hand to either sides of the midline and gently elevating the lateral fornix up to the abdominal hand a right and left adnexal mass should be

palpated. The pouch of Duglas is also carefully assessed for nodularity or tenderness (endometriosis, PID, metastatic carcinoma). It is usually impossible to feel normal tube and ovary, left adnexal masses are more difficult to evaluate than right one because of the position of sigmoid colon on the left side of the pelvis.

Rectal Examination

A rectovaginal examination is helpful in evaluating masses in cul-de-sac, the rectovaginal septum, parametrium, or adnexa. It's also used for examination of the girls and in case of external genitalia atresia.

Investigations

Include appropriate and special laboratory test and instrumental methods of examination.

Bloodworks:

>comlete blood count, erythrocyte sedimentation rate, blood biochemical tests, blood coagulation indicators

>BhCG for investigation of possible pregnancy or ectopic pregnancy, work-up for gestational trophoblastic neoplasia

>Hormones (FSH, LH, TSH, PRL, estardiol, progesteron, testosteron...) for diagnostic of amenorrhea, menstrual irregularities, menopause, infertility

>immunoferment analysis of STI, tumor markers

Serological diagnostic tests help to identify specific antibodies to the antigens of the pathogens.

Urinalysis

Screening/diagnostic procedures done at the time of gynecological examination:

>examination of the vaginal/cervical/nipple discharge, saline preparation; KOH preparation; Gram staining

For evaluation of the microscopic examination of the vaginal smear it is important to study the vaginal epithelium, the presence of microbiological contamination, leukocyte reaction using a 4-point system to determine the number of microbal cells in a single field of view (Nugent criteria):

+less than 10 microbal cells in a single field of view

++ 11-100 microbal cells in a single field of view

+++ 100-1000 microbal cells in a single field of view

++++more than 1000 microbal cells in a single field of view

>PCR tests for diagnostic of STI. It is a method of identification of nucleic acids. The feature of this method is multiplication (replication) of DNA fragment that is specific for exact type of pathogen with a special DNA-polymerase enzyme. PCR diagnostic advantage is the simplicity of the investigation, full automation; speed of obtaining results, small amount of material is needed for research, the ability to determine the latent and persistent non-culturable forms of pathogens.

>culdocentesis

>endometrial sampling

>Pap-smear

Papanicolaou (Pap) smear is a method of cervical screening used to detect pre-cancerous and cancerous processes in the cervix. Both the endocervical canal and the ectocervix should be sampled when taking the Pap-smear. New tchnologies-

automated liquid-based slide-preparation systems have been developed to decrease false-negative rate for pap-smears.

All women undergo an annual Pap-smear, within 3 years of sexual intercourse, or by age 21.Annual screening should occur until 30 years. Then once in 2-3 years if there have been three consecutive negative tests .If pozitive-annual screening is indicated.

>test functional diagnostics are used for definition of hormonal status research of ovarian function, and include pupil phenomena, fern test, mucus stretching test and basal temperature.

To determine the basal temperature it is necessary to perform the measurement of morning rectal temperature at the same time of the day before getting up in the supine position, before food and liquid intake, smoking using the same thermometer .The measurement is carried out during 2-3 menstrual cycles in absence of acute inflammatory diseases and hormones intake.

At physiological menstrual cycle before the day 14 (proliferative phase) the hypothermia is marked. Starting from the day 14 (luteal phase) the basal temperature increases on 0.4-0.8 'C and stays in the same level no less than 10 days. Presence of two-phased basal temperature reflects the ovulatory menstrual cycle .It is the most common method for evaluation of the functional activity of the ovaries.

Imaging

>ultrasound

>hysterosalpingography: After the the contrast is introduced through the cervix into the uterus, series of X-ray images are made. This method is used for the evaluation of size, shape, configuration of the uterus, tubal patency or obstruction.

>sonohysterosalpingography: Infusion of the saline solution into the endometrial cavity under U/S vizualization expands endometrium, allows vizualization of the

uterus and fallopian tubes. It is useful for investigation of abnormal uterine bleeding, uncertain endometrial findings, infertility, and congenital abnormalities.

>CT/MRI. These methods are useful for diagnostic of tumors of reproductiv organs and pituitary gland.

Genital Tract Biopsy

>vulvar biopsy

>vaginal and cervical biopsy

>endometrial biopsy

Colposcopy

It is a diagnostic procedure of detailed and accurate examination of the cervix .If functions as a lighted binocular or monocular micriscope to magnify the view of the vagina, cervix and vulva. The magnifying possibility of the colposcope is 2 x30 times .Green filter is used to identify certain vascular patterns that may indicate the presence of more advanced pre-cancerous or cancerous lesions .A modern colposcopes equipped by the camera is used to capture images of the cervix before and after treatment. Colposcopy is used both for diagnostics and treatment of cervical lesions.3% Acetic acid (Schiller's)solution and 5% iodine solution (Lugol's) are applied to the surface of the cervix to improve visualization of abnormal areas.

Areas of the cervix which turn white after the application of acetic acid or have abnormal vascular pattern, also areas that didn't color by iodine solution are often considered for biopsy.

Treatment for significant lesions includes loop electrical excision procedure, cryotherapy, and CO2 laser ablation.

Chapter review

1. Which gynecological disease is the most common in children?

A) vulvo-vaginitis

B) Dysmenorrhea

C) Ovarian cysts

D) Endometriosis

E) Uterine myomas

2. Which of the following is not one of the main gynecologic complaints?

A) Tachycardia

B) Abdominal pain

C) Tachycardia

D) Vaginal discharge

E) Abnormal vaginal bleeding

3. Development of secondary sexual characteristics is evaluated by:

A) Tanner scale

B) Apgar scale

C) Burnelt scale

D) Ferriman-Gallwey scale

E) Bethesda system

4. Which organs is bimanual examination provide information about?

A) uterus and adnexa

B) Vagina

C) Cervix

D) Ovaries

E) Fallopian tubes

5. True or false? Pap-smear is a method of screening to detect pre-cancerous and cancerous processes in the uterus.

A) True

B) False

Chapter 2.Female Reproductive Anatomy

2.1 Anatomy of External Genitalia

Development

The reproductive organs are developed from the intermediate mesoderm. Before the 7 week of gestation, the appearance of the external genital area is the same in the males and females. This includes the development of a genital tubercle and a membrane dorsally to it, covering the developing urogenital opening, and the development of labioscrotal folds. Ventrally and caudally, the urogenital membrane differentiates into the genital folds laterally and the urogenital folds medially. The labioscrotal folds form the labia majora in females, whereas the urogenital folds develop into the labia minora. The ramainder of the phallus forms the clitoris.

External Genitalia

The external genital organs include the mons pubis, labia majora, labia minora, Bartholine glands, clitoris and the perineum. The area containing these organs is called the vulva. (Figure2-1)

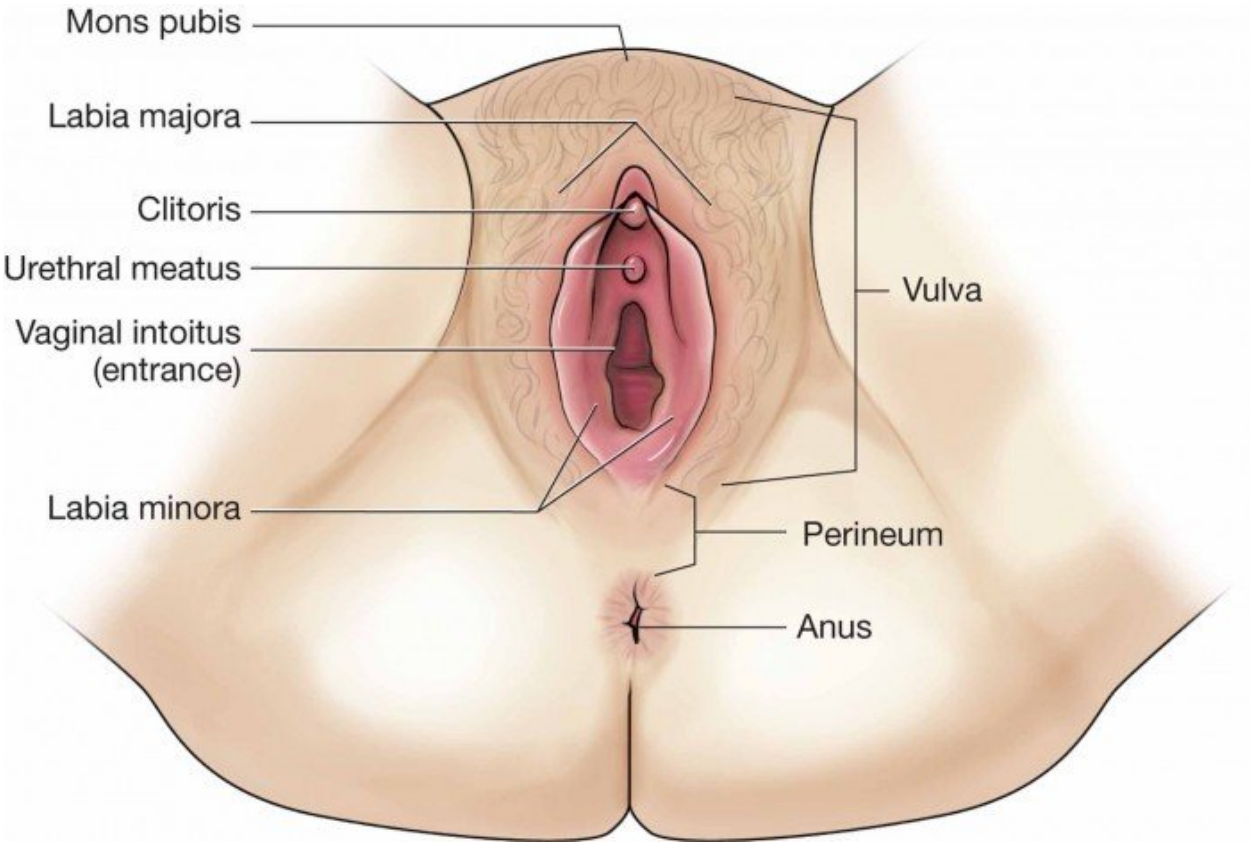


Figure 2-1 Female external genitalia

The mons pubis

It is an area that covers the pubic bone and rich of fatty tissue. During puberty, it becomes covered with hair.

The labia majora are the most prominent element of the vulva, which enclose and protect the other external genital organs. They are large, hair-covered folds of skin that contain subcutaneous fat and sebaceous glands that produce lubricating secretions.

The labia minora lie just inside the labia majora and surround the introitus of the vagina and the urethra. The labia minora contain no hair, but have rich supply of venous sinuses, sebaceous glands and nerves. The shape and the size of labia minora vary from barely noticeable structure to leaf-like flaps. Anteriorly they united over the clitoris.

The clitoris lies between the labia minora just at their upper united end. It locates in front of the urethra and consists of the glans, the body and the crura. It corresponds to the penis in the mail. Only the glans clitoris is visible externally. The body, which is composed of a pair of corpora cavernosa, extends superiorly for a distance of several centimeters and divides into two crura, which are attached to the undersurface of either pubic ramus. It is rich by the blood vessels.

The opening of the vagina is called the introitus. The introitus is bounded by the hymen. Usually, the hymen is represented by the circle of carunculae myrtiformes. It may take many forms.

Bartholin's glands are situated just posterior to the vestibular bulbs in the both sides of the vaginal introitus. Their ducts empty into the the introitus just below the labia minora. They are often the site of gonococcal infections and painful abscesses.

The perineum is the region between thighs inferior to the pelvic diaphragm. It is the inferior boundary of the pelvis. Anteriorly, the perineum extends to the symphysis pubis. Posteriorly, it is bounded by the ishcial tuberosities, the sacrotuberous ligaments, and the coccyx. The perineum has a roof formed by the pelvic diaphragm and a floor of fascia and skin. It has a diamond shape and can be divided into two triangles by the perineal muscules cross the the pelvic outlet between the two ishcial tuberosities and come to the perineal body: urogenital triangle anteriorly and anal triangle posteriorly.

The anterior vulva is innervated by anterior labial nerves (branches of the ilioguinal and genital branch of the genitofemoral nerves). Posterior (labial) nerves supply the labia minora, vagina, and clitoris (dorsal nerve of the clitoris).

Blood flow to the vulva is provided by external and internal pudendal arteries.Blood is returned by the labial and internal pudendal viens.Lymph drains into the superficial inguinal lymph nodes, deep inguinal nodes, and internal iliac nodes.

2.2 Anatomy of Internal Genitalia

The internal female genitalia include the vagina, uterus, ovaries and Fallopian tubes (Figure 2-2)

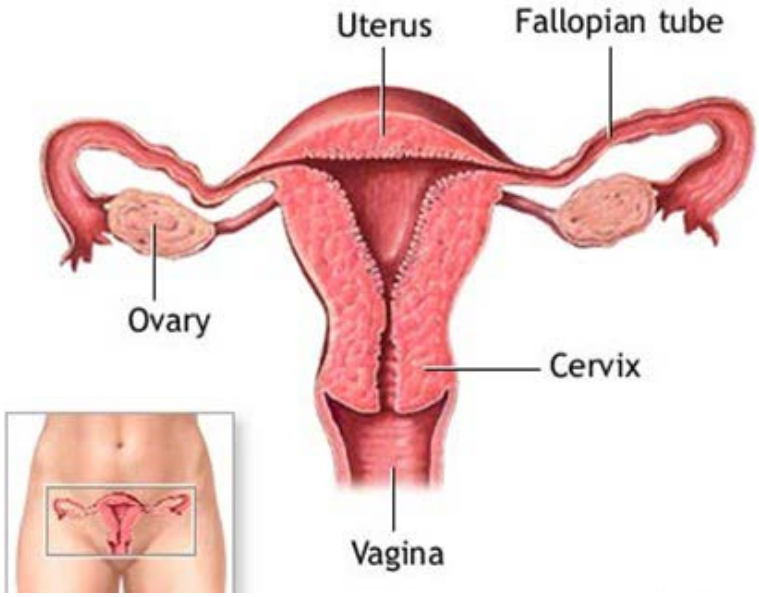


Figure 2-2 Female internal genitalia

The differentiation of the internal genitalia starts from the 7th weeks of embryogenesis. The upper vagina, cervix, uterus and fallopian tubes are formed from the paramesonephric (mullerian) ducts. The paramesonephric duct is formed from a finger-shaped invaginaion of the coelomic epithelium on the upper pole of the mesonephros. Each paramesonephric duct opens into the coelomic cavity cranially (future ampula of the fallopian tube).The paramesonephric duct invades on both sides into the mesonephros and grows in the caudal direction. The blind distal end of each paramesonephric duct crosses over the mesonephric duct in order to grow further medially. There two paramesonephric ducts fuse terminally at the urogenital septum, forming the uterovaginal primordium, the distal point of which is known as mullerian tubercle. Further dissolution of the septum between

the fused paramesonephric ducts leads to development of the uterus, cervix and the upper vagina.

Differentiation of gonadal tissue occurs anterior to the mesonephros and along the entire medial aspect of the urogenital ridge. The cranial portions of the gonadal ridge degenerate, leaving an indifferent genital gland near the mesonephros. Nearly 3 weeks of gestation primitive germ cells appear intermixed with other cells in the epithelial lining of the dorsal part of the primitive hingut. These germ cells migrate to the gonad and are seen as a radial strands extending into the mesenchymal tissue. The migrating cells consist of primordial egg cells and prospective granulosa cells.

Vagina

The vagina is an elastic flattened muscle canal that extending from the hymenal ring to the cervix.It is located in the pelvic cavity posterior to the bladder and anterior to the rectum.The inner surface of the vagina is folded to provide greater elasticity and covered by nonkeratinized stratified squamous epithelium.Deep to the epithelial layer is a lamina propria,alayer of connective tissue with many elastin fibers that allow vagina to stretch.A layer of smooth muscles located under the lamina propria.The outermost layer of the vagina is known as tunica externa,it forms the outer protective shell of the vagina.It connects with the cervix by fornices.The posterior fornix is deep and has immediate proximity to the pouch of Douglas .And thereby , allows easy access to the peritoneal cavity from the vagina during culdocentesis or colpotomy.

Blood is supplied to the vagina by the uterine and vaginal arteries,both branches of thr internal iliac artery.Venous return is achieved by the vaginal venous plexus, which drains into the internal iliac veins.Lymphatic drainage is via the iliac and superficialinguinal lymph nodes.

Uterus

The uterus is a pear-shaped organ, divided into the body and cervix: a thin segment, the isthmus, joines them. It locates in the pelvic cavity between the urinary bladder anteriorly and the rectum posteriorly. The average dimensions are approximately 8 cm long, 5 cm across, and 4 cm thick.

The uterine wall consists of 3 layers:

-the inner layer ,endometrium ,is highly specialized and essential to menstrual and reproductive function.It may vary from 2 to 10 mm in thickness,depending the stage of menstrual cycle

-the middle layer,myometrium ,is the muscular layer.It is arranged in three defined layers:a thin outer of longitudinal muscle,a thick layer of spiral myometrial fibers and an inner layer of poorly defined circular muscle surrounding the ostia of the fallopian tubes and the internal and external ora of the cervix

-the outer layer of the uterus, the serosa or perimetrium, is a thin layer of tissue made of epithelial cells, mostly of peritoneal mesothelium

The cervix is generally 2-3 cm in length.The ectocervix is covered with a nonkeratinized squamous epithelium, and endocervix is covered with simple columnar epithelium.

The uterus normally lies in anteversion and anteflexion and is held in place by muscular and fibrous support.The important muscular supports are the levator ani miscules and the perineal muscules. Four paired sets of ligaments are attached to the uterus:

1. Anteriorly, the round ligaments,which stretch from the top of the uterus just in front of the fallopian tubes ,enter the inguinal canal and terminate by fusing with the pubic orifice.The round ligament has small supportive value ,but help to keep uterus anteverted.

2. Lterally, the cardinal ligaments.They extend from the pelvic fascia on the lateral pelvic walls and insert into the lateral portion of the cervix and vagina,reaching to the level of the isthmus.It is one of the structures preventing uterine prolapse.

3. Posteriorly, the uterosacral ligaments, which are thinner and less effective as a support.They arise from the sacral fascia and insert into the posteroinferior portion of the uterus above the isthmus.

4. The pubocervical ligaments, which pass anteriorly around the bladder to the posterior wall of the pubic symphysis.

The broad ligaments,which pass from the side of the uterus to the lateral walls of the pelvis ,help to hold the uterine fundus in anteversion and has no major support function.The fold of the broad ligament containing the fallopian tube is called mesosalpinx.

The uterus is partially covered by the peritoneum.Anteriorly it descend from the posterior wall of the bladder and cover the uterine fundus, forming a fold between the bladder and the uterus.This space is called vesicouterine space. Posteriorly the peritoneum descends the posterior wall of the uterus and covers the rectum. This fold of the peritoneum is deeper and has very important anatomical significance. This space is called the Douglas pouch.

Blood is provided to the uterus by the ovarian and the uterine arteries, the latter of which arise from the anterior division of the internal iliac artery. The uterine artery gives off the vaginal artery (althrought this is usually a separate branch of the internal iliac artery), which supplies the upper vagina.

Lymphatic drainage of the uterus and upper vagina is primarily to the obturator and internal and external iliac nodes.

Fallopian tubes

The fallopian tubes are bilateral muscular structures that connect the uterine cavity with the peritoneal cavity. They are 7 to 12 cm in length and usually less than 1 cm in diameter. They are enclosed to the superior margin of the broad ligament.Fallopian tubes consist of three parts: interstitial portion, isthmus and ampullary portion.

The tube begins in the uterine cavity at the cornu and penetrates the myometrium - interstitial portion. The medial portion of the tube is located superiorly to the round ligament, anterior to the ovarian ligament and fixed in position. This part has a narrow lumen and is reffered to as the isthmus. The length of this part is about 2-3 cm. The ampulla is the largest and longest portion of the tube, approximately 5 cm in length. This portion of the tube is suspended from the broad ligament by the mesosalpinx and is quite mobile.The mobility of the fimbriated end of the tube plays an important role in infertility. The ampula is a site for most ectopic pregnancies.

The wall of the tubes is presented by three layers of musculature: the inner longitudinal, the middle circular, and the outer longitudinal layer. The tubes are lined by a ciliated, columnar epithelium, which is responsive to the estrogen and progesterone levels during the menstrual cycle.

The blood supply of the tubes is from the upper end of the uterine artery that anastomoses with the ovarian artery. The venous system accompanies the arterial distribution. The lymphatic drainage runs to the para-aortic or lumbar nodes.

The ovaries

The ovaries are glistening, oval in shape, flattened organs about 4x2x2 cm in size, with the weigth of 3-8 g. They are situated on the superior surface of the broad ligament and are suspended between the ovarian ligament medially and the infundibulo-pelvic ligament laterally.

Histologically the ovary is divided into the outer cortex and the inner medulla. The cortex consists of a cellular connective tissue and the stroma. The medulla is

composed of soft connective tissue which containes blood vessels and nerves. The cortex is surrounded by the germinal epithelium. The ovaries contain 1-2 million oocytes at birth.

The blood supply is from the long ovarian arteries, which arise from the abdominal aorta just below the renal arteries. The venous drainage from the right ovary is directly into the vena cava inferior, from the left ovary is into the left renal vien. The lymphatic drainage of the ovaries passes via the infundibulopelvic ligaments to the pelvic and para-aortic nodes.

2.3 Development Abnormalities of Genital Tract

Female genital abnormalities are uncommon and often do not present until puberty. They may be isolated or associated with chromosomal or metabolic disorders.

Congenital anomalies of external genitalia are quite variable. Ambiguous genitalia can present with clitoromegaly, bifid clitoris, midline fusion of the labiosacral folds. Labia minora abnormalities may be presented with labial fusion or hypertrophy. Hypertrophy can be unilateral or bilateral and may occasionally require surgical treatment. Abnormalities of labia majora as the hypoplasia or hypetrophia are usually associated with ambiguous genitalia of female pseudohermaphroditism due to congenital adrenal hyperplasia. Because of genetic defect in the synthesis of the enzyme 21-hydroxylase that is required for cortisol synthesis, adrenal glands secrete abnormally large amounts of virilising steroids. Androgen-producing tumors of the ovary or adrenal gland also cause this problem. The child is borned with enlarged clitoris and fused sacrolabial folds. Normally, a single urinary meatus at the base of the phallus is seen with the vagina entering a persistent urogenital sinus. Internal genital development is normal.

True hermaphroditism is characterised by presense of both ovarian and testicular tissue in a single patient. Chromosomal examination shows presence of a single Y chromosome even with more than a single X chromosome. No single clinical

feature can distinguish true hermaphroditism from other forms of intersexuality with firm diagnosis possible after ultrasound and hormone assay.

Male pseudohermaphroditism may occur with varying degree of virilisation and mullerian development. This is most commonly the result of genetic mozaicism, such as 45 XO/46XY. Also causes include abnormal or absence of gonadotropin secretion, defect in biosynthesis of testosterone, androgen insensitivity syndrome or 5-alfa reductase deficiency. Genetically male infants with abnormal or ectopic testes may have external genitalia so ambiguous that true sex cannot be identified. May also be indistinguishable from a normal female or, in others, may appear as hypospadic male. These patients can also have a vagina, cervix, uterus and fallopian tubes; ovaries are usually absent.

Abnormalities of the hymen often presented with imperforated hymen. It may be either congenital or acquired from inflammatory. It is initially manifested with obstruction of menstrual flow after puberty.

Abnormal embryologic development of the ovaries is uncommon. Congenital duplication or absence ovarian tissue may occur, as may ectopic ovarian tissue or supernumerary ovaries. Ovarian agenesis is a result of wide range of chromosomal anomalies characterized by the absence of two X chromosomes that results in the production of streak ovaries, and is associated with a number of other somatic abnormalities. Most common cause is a Turner syndrome (45XO). Turner's syndrome is now used to describe girls with sexual infantilism with ovarian streaks, short stature and two or more of the following: shield chest, obesity, high palate, low-set ears, hypoplasia of the nails, osteoporosis, lymphoedema, hypertension, coarctation of the aorta, general learning disability, deafness, micrognathia, hyperpigmentation, keloids. Women with Turner's syndrome usually progress through puberty and develop secondary sexual characteristics, but enter menopause shortly thereafter.

Uterine abnormalities are the most common abnormalities of female reproductive organs. They affect woman's fertility, and can cause uterine bleeding and abdominal pain. The most common types of uterine abnormalities are caused by incomplete fusion of the Mullerian or paramesonephric ducts. Paramesonephric ducts first develop at 6 weeks of gestation lateral to the cranial pole of the mesonephric duct as a result of absence of Y chromosome and Mullerian inhibiting substance, which leads to the regression of mesonephric ducts. By 9-10 weeks they fuse in the midline at the urogenital septum to form the uterovaginal primordium. Further dissolution of this septum leads to the development of the single uterus and cervix. Complete failure in fusion of the Mullerian ducts is rare and results in double vagina, double cervix and double uterus (uterus didelphys). The most common anomalies of the uterus result from either incomplete fusion of the paramesonephric ducts or incomplete dissolution of the septum or formation falure. (Figure 2-3)

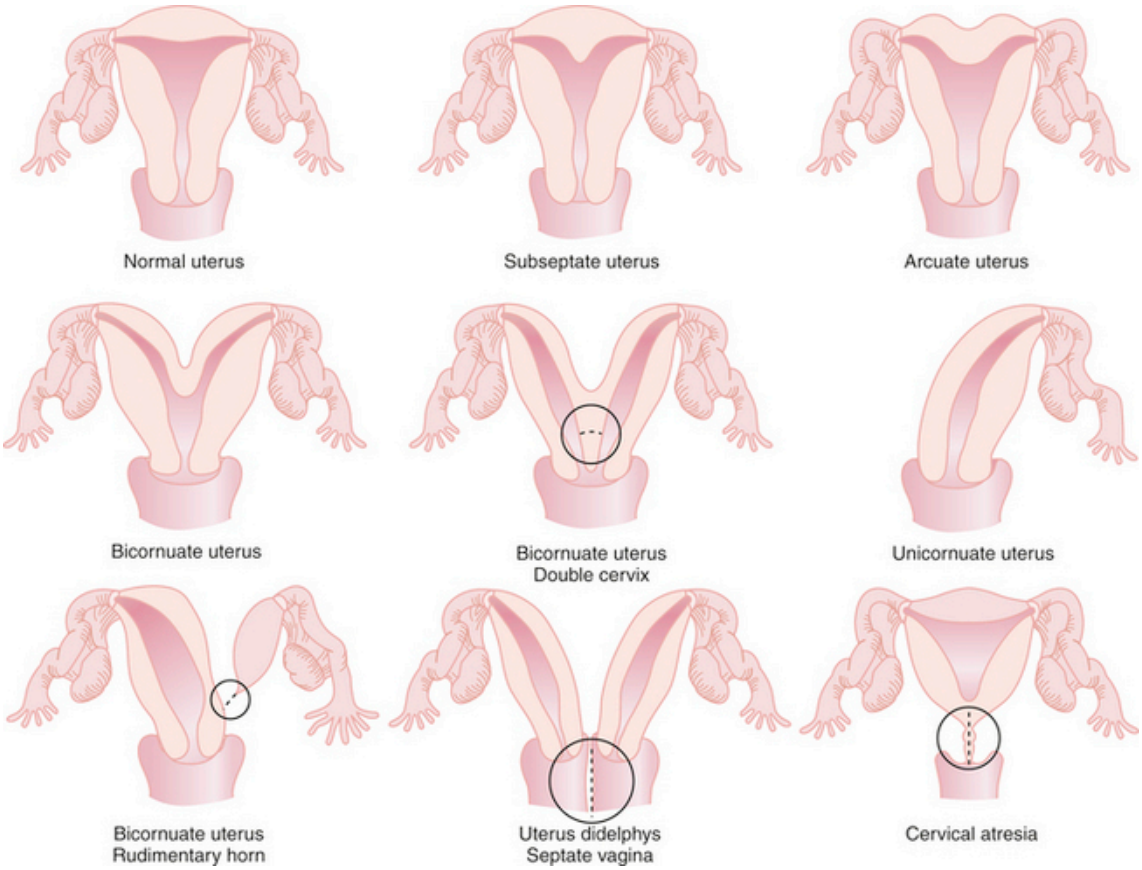


Figure 2-3 Variations of uterine and cervical development.

Failure of fusion is most evident in uterus didelphys. A bicornuate uterus with a redumentary horn and bicornuate uterus with or without double cervix are also representing a fusion falure. Incomplete dissolution of the septum results in septate, subseptate, arcuate and bicornuate uterus. Falure of formation can be observed in the unicornuate uterus. Complete lack of development of the paramesonephric system women generally have incomplete development of the fallopian tube associated with the absence of the uterus and most of the vagina. Usually these types of anomalies are assosiated with the anomalies of the urinary system.

Congenital abnormalities of the cervix are due to failure of fusion of the Mullerian ducts, resulting in a duplicated or septate cervix. Congenital absence or hypoplasia of the cervix may be associated with urinary tract or musculoskeletal (spinal) abnormalities.

Isolated anomalies of fallopian tubes are rare. Usually they associated with the abnormal development of paramesonephric ducts. Abnormalities of the tubes may be presented by their aplasia or atresia, complete or distal duplication. Women, exposed diethylstillbestrol, may have structural abnormalities of the fallopian tubes, uterus and cervix. They presented by shortened, distorted, or clubbed fallopian tubes, small, T-shaped endometrial cavity and deformity of the cervical canal.

Chapter review

1. Which structure is developing to the labia majora in females during the embryogenesis?

A) Labioscotal folds

B) Urogenital folds

C) Remainder of the phallus

D) Genital tubercle

E) Mullerian duct

2. Wich arteries are blood flow to the vulva provided by?

A) Internal and external pudendal arteries

B) Obturator arteries

C) Internal iliac artery

D) Uterine arteries

E) Rectal artery

3. Which structure is not formed from the paramesonephric duct?

A) Vulva

B) Upper vagina

C) Fallopian tubes

D) Uterus

E) Cervix

4. What kind of epithelium is the vaginal internal surface covered by?

A) Nonkeratinized stratified squamous epithelium

B) Keratinized squamous epithelium

C) Columnar epithelium

D) Ciliar epithelium

E) Mesothelium

5. Which of the following is the potential space between the anterior surface of the uterus and the posterior wall of the bladder?

A) Vesicouterine space

B) Rectovaginal septum

C) Morison pouch

D) Douglas pouch

E) Isthmus

6. The uterine artery is a main branch of which of the following vessels?

A) Internal iliac artery

B) External iliac artery

C) Common iliac artery

D) Iliolumbar artery

E) Aorta

7. Which of the following is the correct progression of the fallopian tube anatomy from proximal (uterus) to the distal (fimbria)?

A) Isthmus, ampulla, infundibulum, fimbriae

B) Isthmus, infundibulum, ampulla, fimbriae

C) Infundibulum, ampulla, isthmus, fimbria

D) Ampulla, infundibulum, isthmus, fimbriae

E) Isthmus, ampulla, fimbriae, infundibulum

8. Which syndrom is the most common cause for ovarian agenesis?

A) Turner’s syndrome

B) Cushing's syndrome

C) Edward’s syndrome

D) Down's syndrome

E) Rokitansky syndrome

9. This type of uterine abnormality is developing as a result of complete failure in fusion of paramesonephric ducts:

A) Uterus didelphys

B) Septate uterus

C) Unicornuate uterus

D) Bicornuate uterus

E) Arcuate uterus

10. Women exposed Dyethylstillbestrol have structural abnormalities of the following organs exept:

A) Labia majora

B) Fallopian tubes

C) Uterus

D) Cervix

E) Endometrial cavity

Chapter 3 Puberty and Disorders of Pubertal Development

Function of reproductive organs of women is most exposed to age-related changes. Based on the biological characteristics of the female organism there are the following periods of a woman's life:

I.Prenatal period (embryonal, fetal)

II.The neonatal period and childhood (neonatal period-first 10 days of life and childhood period till 8 years old)

III.Puberty (8-16 years)

IV.Reproductive period (17-45 years)

V.Perimenopause (45 year till the onset of menopause)

VI.Menopause

VII.Postmenopause (2 years after the onset of menopause)

VIII.Senile period

Puberty is the basis for the formation of the reproductive function of girls. There is a variety of factors influencing and determining the characteristics of puberty.

The average frequency of violations of puberty is about 15-18%. The investigations found out that in the structure of pathologic puberty there is a domination of an inflammatory diseases of reproductive organs (63%), violations

of menstruation and menstrual cycle (2.5-29%) with a tendency to increase. It should be noted that a high incidence of abnormal puberty is manifested in delayed puberty, and less in precocious puberty.

3.1 Physiology of Puberty

Puberty is a period of age that encompasses the development of secondary sexual characteristics and capacity to reproduce. The word puberty is derived from Latin "Pubertas", that means adulthood. During this period a variety of endocrinologic, physical, and psychological changes occure. Physical changes are regulated by changes in the levels of hormones of the pituitary gland-luteinizing and folliclestimulating hormones.

The average age for the first signs of puberty is 8-10 years. The first change of puberty is usually the start of breast development. This change occurs around 8-13years. Afterwards, pubic and underarm hairs begin to grow. The interval between the breast budding and menarche is about 2-3 years. That's mean that average age for menarche is 10-12 years.

The onset of pubertal changes is depended on several factors that influence the physical development of girls such as:

>Nutritional status: Puberty tends to have early beginning in obese children, whereas in girls who are underweight and malnourished puberty tends to start later.

>Genetics: Puberty tends to start earlier in girls whose mothers matured early.

>Psychological factors: Psychotic and neurotic disorders influence the normal onset of puberty, resulting in it delay.

>Ethnic factors: Puberty tends to start earlier in blacks and Hispanics than in Asians and whites.

>Physical exercises: Excessive exercises and low calory intake delay the onset of puberty.

Puberty is initiated by hormonal changes in the hypothalamus, which stimulate the pituitary gland to release gonadotrophins that stimulate the gonads and adrenals. There are exact changes in activity of the hypothalamic-pituitary-gonadal axis during different periods of woman development.

The study of physiology and pathology of the puberty is one of the most important problems of the children and adolescent gynecology. The necessity to define the physiologic indicators of puberty is the basis for the early diagnostic of the pathologic processes of puberty.

The state of health of girls during puberty is determined by the influence of the following factors: peculiarities of their maternal pregnancies, the existence of the birth trauma, high frequency of chronic diseases, mental health, nutritional and environmental factors, stress and excessive physical and educational load.

The basis of puberty is the physical development, including intense growth and weight gain. One of the criteria for starting the menstrual function is the body mass about 44.5+_1.6 kg. There was determined that average annual increase in body growth is 8.3 cm. The most intense growth of girls is observed in 11-12 years, 6-12 month before menarche. The physical development of girls involves a dynamic increase in the body mass, growth, circumference of the chest, span, shoulder width and the external pelvic diameters.

At the same time, the body mass and growth indicators determined by genetic characteristics, and they are individual. Despite the growth in children and adolescent regulated by growth and thyroid-stimulating hormones, it should be noted fundamental influence of sex steroids on the rate of growth of children. It has been proved that low concentrations of estrogen stimulates the growth of the girls, while a high levels of estrogen causes growth arrest, expressed in premature closing of epiphyseal bone growth zone.

According to the studies, 95% of healthy girls has breast enlargement as initial manifestation of puberty (thelarche). 15% of girls the onset of puberty begins with the growth of pubic hair (pubarche). Menarche usually starts within 18-24 month after the onset of breast development. The average age for the menarche is 12.5 years.

Puberty is determined by the formation of the functional activity of the hypothalamic-pituitary-ovarian system. Pulsatile secretion of the releasing hormones accompanied by the increase in blood levels of FSH and LH, sensitivity of the ovaries to these hormones, and, accordingly by the development of the follicular unit of the ovaries.

Before the onset of puberty, the low level of sex steroids inhibits functional activity of the hypothalamus and pituitary gland. In prepubertal period hypothalamic sensitivity to the action of sex steroids reduces, that apparently indicates the beginning of puberty. The first hormonal sign of puberty is manifested by the increasing of the pulsatile release of gonadotropin-releasing hormone during sleep. Increasing of releasing hormone level leads to increasing of FSH and LH concentration in the adenohypophysis. Pulsatile secretion of gonadotropin-releasing hormone is repeated every 60 to 90 minutes. This rejime of gonadotropin secretion is manifested by the pulsatile secretion of LH and FSH, which stimulates follicular growth in ovaries.

In the middle of puberty with the beginning of ovulatory cycles the mechanism of positive feedback established. The key point of this process is a significant increase in FSH and LH levels, in response to small concentration of estrogen. An intense increase in estrogen level causes dramatically increases in FSH and LH levels that lead to ovulation.

Clinical manifestation of the onset of puberty is breast enlargement with subsequent appearance of pubic and axillar hair. Breast development starts at 10-14 years, and manifested by proliferation of the ducts and alveols, appearance of

spesific fat deposits. In the early stages of the breast enlargement there is a bulding of the mammal gland under the chest, with the following appearance of nipple bulge and increasing of the areola observed. Stages of breast development are assessed by the Marshall and Tanner's scale. (Figure 3-1, Table 3-1)

Tanner stage	FEMALES		MALES	
	Breasts	Pubic hair	Genitalia	Pubic hair
1	Nipple elevation only	None	Testicles 1-2 cm	None
2	Small raised breast bud	Growth along labia, sparse, lightly pigmented	Testicles >2 cm, scrotal enlargement	Sparse, lightly pigmented
3	Breast and areola enlarge with no contour difference	Increases in amount, darkens, starts to curl	Testicles continue to enlarge, penis lengthens	Increases in amount, darkens, starts to curl
4	Further enlargement with areola and nipple projecting to form secondary mound	Resembles adult type, but not spread to medial thighs	Scrotum darkens, widening of glans penis	Resembles adult type, but not spread to medial thighs
5	Adult contour with areola and breast in same contour, nipple protruding	Spreads to medial thighs, adult distribution	Adult size and morphology	Spreads to medial thighs, adult distribution

Table 3-1 The Marshall and Tanner scoring system

The appearance of pubic and axillar hair is stimulated by the hormones of adrenal gland: DHEA, DHEA-S and androstenedione. The synthesis of androgens is influenced by the adrenocorticotropic hormone (ACTH). It should be noted, that to date the pathogenetic mechanism of androgen level increasing remains unclear.

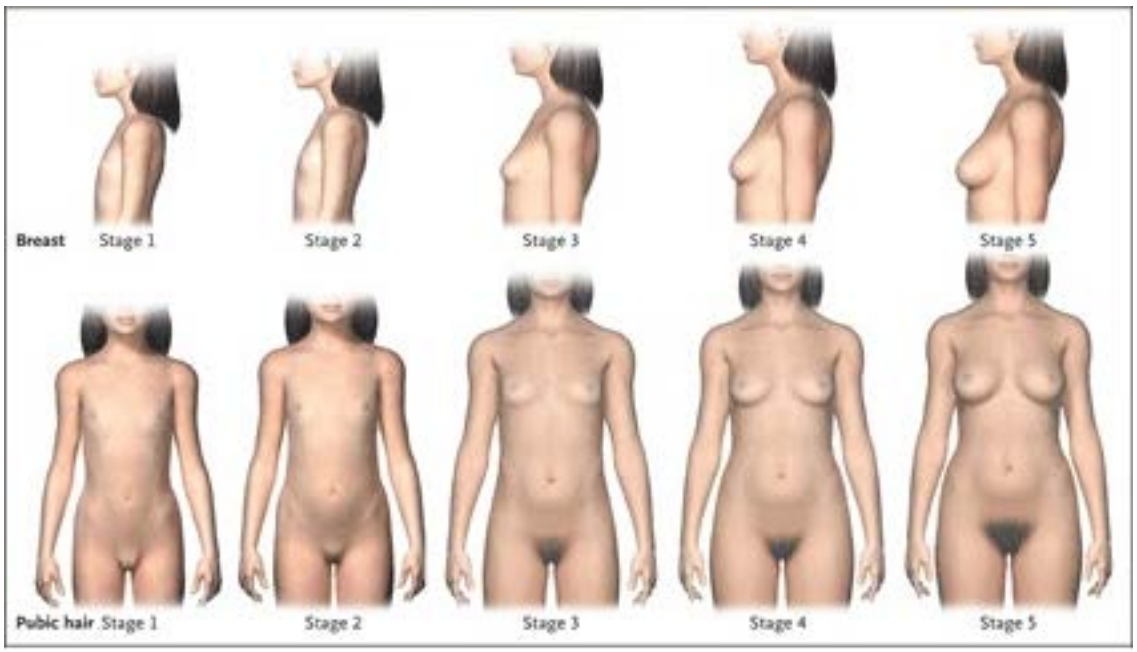


Figure 3-1 Stages of breast and pubic hair development according to Marshall and Tanner scoring system

Puberty includes the growth and formation of the functional activity of the organs of reproductive system.

There is increasing in size and thickness of labia majora and labia minora under the influence of estrogens. This process terminates with the onset of menarche. Along with the development of the labia the hymen develops. It becomes thick, the diameter of the hymenal opening increases to 10 mm. Bartholin's gland start their mucus secretion. This period is marked by the enlargement of the clitoris.

In puberty vaginal epithelium is formed: it becomes dense, pink with uneven surface and folds. Functional activity of the vagina is also change and manifested by the mucus secretion by the vaginal epithelium, decreasing of Ph, which results in reducing of the vaginal resistance to the pathogenic microbs.

With the start of estrogen synthesis the development of the uterus-the main target organ of the reproductive system, takes place. Primarily, there is evidence in icreasing of the length of the uterus, and the thickness of myometrium due to hyperplasia and hypertrophy of muscle tissue. The single-layered cubic epithelium

replaced by the multilayered columnar epithelium. The columnar epithelial cells of the cervix start to produce mucus. According to the sonography, the angle between the uterine body and the uterine cervix becomes more distinct, the correlation between the length of the uterine body and the cervix is about 2:1.

During the puberty the ovaries increase in their size and change their location. To the end of puberty the size of the ovaries is approximately 3,0 x 2,1 x 3,0 and they locate in the pelvic cavity 2-4 cm above and behind the uterine angles.

The ultimate sign of puberty is the menarche. The average biological age for menarche is 12.5 year at body mass 47.8+_ 6.9 kg and daily estrogen blood concentration 10 mg.

Thus, under the influence of the increasing activity of the hypothalamo-pituitary-ovarian system there is a sequence of formation of secondary sexual characteristics, and the formation of menstrual function, what is the basis of physiological puberty.

3.2 Pathology of Puberty

Precocious Puberty

Precocious puberty refers to the appearance of physical and hormonal characteristics of pubertal development at an age earlier than considered normal.

Recently, puberty was considered precocious in girls younger than 8 years; but studies indicate that signs of precocious puberty often present in girls aged 6-8 years. The incidence of precocious puberty is about 0.5 % in whole population, and 2.5-3.0% of all children and adolescent gynecological pathology .The incidence of precocious puberty in North America is 1 in 10000 children ,and it is 5 time more common in girls. There is no clear tend toward earlier puberty in northern Europe, but earlier mean age of menarche has been reported in southern European countries.

Racial factors also affect the incidence of precocious puberty, so black girls have the onset of breast development and pubic hair growth gabout one year earlier than white girls. In 75 % of cases of precocious puberty in girls, the cause is idiopathic.

Early onset of puberty can cause several problems. The early onset of puberty in girls can cause tall stature, greater than in their peers, followed with rapid bone maturation and premature fusion of the long-bone epiphysis, which result in short adult stature. The early development of secondary sexual characteristics and menses may promote psychosocial problems for the child, manifested in poor self-esteem, high anxiety, irritability and withdrawal.

Classification

I. True Precocious Puberty

1. Idiopathic -early maturation of entire hypothalamic-pituitary-gonadal axis

2. Central nervous system abnormalities associated with the excessive secretion of gonadotrophins or failure in regulation of hypothalamic-pituitary system:

a) Tumors

b) Hypothalamic hamartomas

c) Brain trauma

d) Congenital anomalies

II. Pseudo- Precocious Puberty

1. Isosexual:

a) estrogen-producing ovarian neoplasm

b) estrogen-producing adrenal neoplasm

c) Iatrogenic

2. Heterosexual:

a) Congenital adrenal hyperplasia

b) androgen-producing ovarian neoplasm

c) androgen-producing adrenal neoplasm

III. Incomplete Precocious Puberty

1. Isolated premature thelarche

2. Isolated premature adrenarche

The onset of puberty is caused by the secretion of high-amplitude pulses of gonadotropin-releasing hormone (GhRH) by the hypothalamus. High-amplitude pulses of GhRH cause pulsatile increase in the pituitary LH and FSH. Increased LH levels stimulate production of sex steroids by ovarian granulosa cells .Pubertal levels of androgens and estrogens cause physical changes of puberty, including breast enlargement. These levels also mediate the pubertal growth spurt. Increased FSH levels cause enlargement of the gonads and promote follicular maturity.

Complete precocious puberty results in the development of the full complement of secondary sexual characteristics and increased levels of sex steroids. In 75% of cases true precocious puberty is idiopathic. A GhRH stimulation test is positive. In about 10 % of girls with the true form of precocious puberty, a central nervous system disorder is underlying cause. This includes tumors, obstructive lesions, granulomatous diseases, infective processes, head trauma. These conditions

interfere with the normal inhibition of hypothalamic GhRH release. Children with precocious puberty secondary to organic brain disease often exhibit neurologic symptoms before the appearance of premature sexual maturation.

Pseudo-precocious puberty characterizes by the elevated levels of estrogens , that cause sexual characteristics maturation without activation of the hypothalamic-pituitary axis .In these girls a GhRH stimulatin test is negative and does not induce pubertal levels of gonadotropins. Causes include ovarian neoplasm, iatrogenic factors (exogenous estrogenic compound use), the McCune -Aldright syndrome (multiple cystic bone defect, cafe au lait spots, adrenal hypercortisolism, hyperthyroidism and acromegaly), prolonged severe hypothyroidism, Peutz-Jeghers syndrome (a rare sex cord tumor with estrogen secreting annular tubules). It should be noted, that when the initial cause of pseudo-precocious puberty is eliminated, some girls go on to develop true precocious puberty.

Heterosexual precocious puberty results from virilizing neoplasms, congenital adrenal hyperplasia, or exposure of exogenous androgens. This type of precocious puberty characterizes by the excessive androgen producing.

Incomplete precocious puberty characterizes by early appearance of an isolated single secondary sexual characteristic. These conditions include premature thelarche, the isolated breast development before the age of 4 years, that is probably secondary to transient estradiol secretion; premature adrenarche, the isolated appearance of axillary hair before the age 7 years that is the result of premature androgen secretion by adrenal gland; and premature pubarche, the isolated appareance of pubic hair before the age 8 years. Sometimes these conditions may be associated with the development of nonclassic adrenal hyperplasia or polycystic ovarian syndrome.

Treatment

Treatment for precocious puberty depends on the cause. Most children with idiopathic causes of precocious puberty, without underlying diseases can be

effectively treated with GhRH-agonist. Long-term GhRH-agonist treatment suppresses pituitary release of LH and FSH, resulting in decline of gonadotropin levels to prepubertal concentration and arrest of sex steroid secretion. This therapy prevents further sex steroid release and accelerated epiphyseal fusion. The final adult stature of girls, receiving GhRH-agonist therapy is depend on their chronologic age, time of diagnosis and initiation of treatment.

Children with precocious puberty with underlying medical conditions require the initial eliminating of the disease that causes this problem. If child has a tumor that's causing precocious puberty, puberty usually will stop with the surgical removing of the tumor. Some types of precocious puberty don't require treatment at all. But emotional support in these children is very important.

Delayed puberty

One of the most frequent pathology of puberty is delayed physical development. Delayed puberty refers to the absence of secondary sexual characteristics at 13 years, and absence of menstruation during 2 years after onset of thelarche. The incidence of delayed puberty in girls is 2-7%. In general, the causes of delayed onset of puberty are the chromosomal abnormalities (43%) and constitutional delay of physical development (10%) that usually tends to be familial. Clinical manifestations of the delayed puberty in girls of 13-15 years old in Azerbaijan is a significant reduction in parameters of physical development, including stature 149,88+_0,13 cm and body mass 43,2+_0,9 kg, I-II degree of severity of secondary sexual characteristics in the absence of menarche.

All the c delayed pauses of delayed puberty can be subdivided into following categories:

I. Constitutional forms of delayed puberty

II. Metabolic disorders:

1. Poor nutrition

2. Obesity

III. Hypogonadotropic hypogonadism:

A. hypothalamic dysfunction (functional insufficiency of hypothalamus):

1. Idiopatic (Kallman syndrome)

2. Brain pathology (Prader-Willi syndrome, trauma, infections, tumors)

3. Functional disorders (systemic diseases, stress, excessive physical load)

B. Pituitary dysfunction:

1. Congenital absence of sella turcika

2. Insufficiency of gonadotropins

3. Trauma

4. Vescular lesions

5. Tumors

IV. Hypergonadotropic hypogonadism:

1. Gonadal dysgenesia

2. Injury of the ovaries (surgery, chemotherapy, radiation, autoimmune oopharitis)

3. Gonadotropins resistance

4. Insufficiency of 16-hydroxylase

V. Hyperandrogenia:

1. PCOS

2. Insufficiency of 17-ketoreductase

3. Cushing’s syndrome

4. Hyperprolactinemia

VI. Other diseases:

1. Mullerian duct agenesia (Rokitansky-Kuster-Mayer syndrom)

2. Congenital abnormalities of the vagina and hymen

3. Insensitivity to androgens

Evaluation of delayed puberty involves the following methods of examination: full history obtain, assessment of the degree of physical and sexual development, examination of external genitalia, laboratory and radiologic evaluation. (Table 3-2)

Table 3-2 Algorithm of patient examination with delayed puberty

A careful history must be taken, with special attention to the patients's past general health, height, dietary habits, and exercise patterns.

Evaluation of anthropometric indicators has a very high diagnostic value. These indicators are: high and body mass, circumference of the chest, span, length of the lower limb, width of the shoulders and external pelvic diameters. Evaluation of the secondary sexual characteristics is performed by the Marshall and Tanner's staging scale.

Gynecological examination of the external genitalia for the assessment of the character of pubic hair growth, anatomical structure of the clitoris, labia, and hymen is one of the important diagnostic criteria.

The study of the characteristics of puberty attaches great importance to the definition of the bone-age of girls. This method is based on X-rays examination of the hands, wrist, distal forearm to determine the presence of ossification points and synostosis between the epiphysis and metaphysis of bones.

Ultrasound examination of the internal genitalia is one of the most common methods of examination in the diagnostic of the pathology of puberty. CT and MRI are performed for the examination of the hypothalamic region and sella turcica.

Treatment of the delayed puberty depends on the cause of the delay, age of patient, and the degree of development of secondary sexual characteristics. When the underlying disorder is the cause of delayed puberty, puberty usually proceeds once the disorder has been treated. An adolescent who is familial late in developing needs no treatment. Sometimes balanced nutrition, appropriate physical examination and supplementation of vitamin A and iron are as efficacious as hormonal therapy in the induction of puberty.

Adolescents with permanent hypoestrogenism require estrogen therapy to complete the development of secondary sexual characteristics. Hormone therapy after establishment of secondary sexual characteristics is required to avoid menopausal symptoms and to prevent osteoporosis. To maximize bone mineral accretion supplementation of calsium and vitamin D are recommended.

At delayed puberty accompanied by growth retardation gonadoliberin is applied. It is administrated intravenously or subcutaneously in pulsed regime every 90 minutes. Girls 17 years and older clomiphene citrate is used. Hormonal therapy is contraindicated at delayed puberty due to deficiency of the body mass.

Genetic disorders cannot be cured, but hormone therapy may help sex characteristics develop.

Chapter review

1. GhRH synthesis is carried out in the:

A) Nuclei of hypothalamus

B) Posterior pituitary

C) Anterior pituitary

D) Neurons of the cortex

E) Substantia nigra

2. The following is characteristic for puberty:

A) Breast enlargement

B) Menarche

C) Appearance of axillar hair

D) Appearance of pubic hair

E) All of the above

3. Causes of precocious puberty may be all of the following diseases exept:

A) Follicular ovarian cyst

B) Brain tumors

C) Congenital adrenal hyperplasia

D) Gonadal dysgenesia

E) Chromosomal abnormalities

4. The incidence of idiopathic precocious puberty is about:

A) 75%

B) 50%

C) 10%

D) 35%

E) 25%

5. This is not characteristic for the precocious puberty:

A) High adult stature

B) Premature breast development

C) Early menarche

D) Premature fusion of the long-bone epiphysis

E) Low adult stature

6. Which symptom is characteristic for the McCune-Albright syndrome?

A) Multiple cystic bone defects

B) Adrenal hypercortisolism

C) Estrogen secreting ovarian tumors

D) Hyperthyroidism and acromegaly

E) Hirsutism

7. Delayed puberty is refers to the absence of the secondary sexual characteristics at:

A) 13 years

B) 10 years

C) 17 years

D) 9 years

E) 15 years

8. Which condition may cause hypergonadotropic hypogonadism?

A) Chemotherapy

B) Injury of the ovaries

C) Chromosomal abnormalities

D) Insufficiency of 17-hydroxylase

D) All of the above

9. What is the pathogenetic basis of hypogonadotropic hypogonadism?

A) Inadequate producing of gonadotropins

B) Functional insufficiency of hypothalamus and pituitary gland

C) 17-hydroxylase deficiency

D) Premature ovarian failure

E) Hyperandrogenia

10. Which of the following methods of examination is not used for the diagnostic of delayed puberty?

A) Bimanual vaginal examination

B) General examination with the evaluation of anthropometric characteristics

C) X-rays of the wrist and distal forearm

D) Blood level of FSH

E) Brain MRI

CHAPTER 4 THE MENSTRUAL CYCLE

4.1 NORMAL MENSTRUAL CYCLE

The menstrual cycle is the series of changes a womans organism goes through in preparation to conception and pregnancy and characterized by cyclical changes in the whole body, most pronounced in the genitals-uterus and ovaries. The average cycle is 28 days,was diagnosed at 60% women. But it is also normal to have a cycle that is shorter or longer, so 21 day cycle was diagnosed at 28%, 30-35 day cycle at 10-12% women. It is important that the length of the menstrual cycle in women was always about the same, that is was a regular.

Each menstrual cycle is a complex interaction among the hypothalamus, pituitary gland, ovaries and endometrium. Normal menstrual cycle is two-phased. During the first phase in the ovary an egg grows and ripens inside a fluid-filled sac called

follicle, which produces estrogens. These estrogens effect on the endometrium causing it's regeneration and proliferation. During the second phase corpus luteum develops in the ovary and it produce progesterone, which in turn causes secretory transformation of endometrium.

In the mid-cycle ovulation occurs. Ovulation – is a mature follicle rupture with the subsequent release of the egg. Then the fully mature egg is delivered into the fallopian tube. If it meets a male sperm, fertilization may take place. If the egg is not fertilized, both it and functional lining of the endometrium are shed in menstrual bleeding. (Figure 4.1-1)

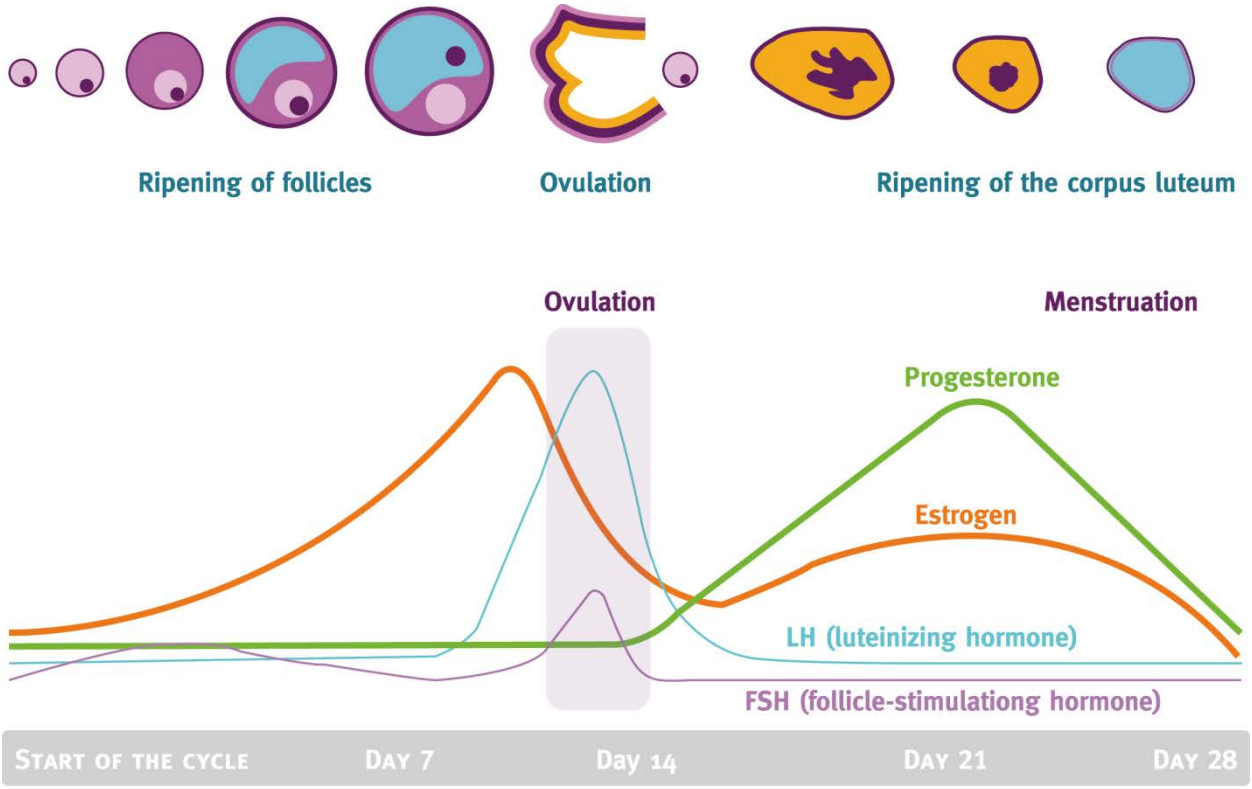


Figure 4.1-1 Normal menstrual cycle

Menstrual cycle is from day 1 of bleeding to day 1 of the next time of bleeding.

Menstruation is a bloody discharge from the genital tract, the first day of which markes the beginning of a new menstrual cycle. First menstruation –menarche

,usually occurs in 12-14 years. Normal menstruation lasts 3-7 days, and in so doing lost 50-150 ml of blood.

Female reproductive system is a functional. It is an integral formation , comprising central and peripheral links which operates on the principle of feedback.

Regulation of the menstrual cycle

Regulation of the menstrual cycle is structured in a hierarchial manner. There are 5 levels of regulation (Figure 4.1-2)

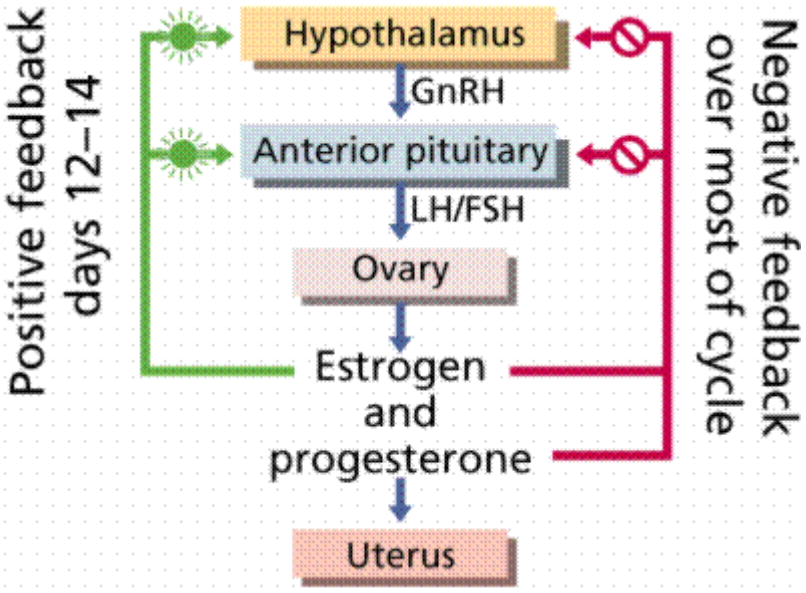


Figure 4.1-2 Levels of regulation of the menstrual cycle

First level are the cerebral structures, in particular cortex.They perceive the impulses from the outside and interoreceptors and pass them through a system of transmitters of nerve impulses to the neurosecretory nuclei of the hypothalamus.

Second level –hypothalamus. It is a structure of brain that regulates the function of the pituitary gland. It consists of cluster of nerve cells which produce special hormones (releasing hormones) and have a direct impact on the syntesis of the gonadotrophins by the pituitary gland. GnRH is a decapeptide that is syntesized

primarily in the arcuate nucleus. It is responsible for the synthesiz and release of both LH and FSH. The secretion of the GnRH is genetically programmed and happens in a certain pulsatile fashion with frequency approximately once per hour. It varies from about 90 minutes in the early follicular phase to every 60-70 minutes in the preovulatory period. During the luteal phase it decreases.

The third level is the pituitary gland. It locates at the base of the brain within a sella turcica and is separated from the cranial cavity by a dura mater. The Pituitary gland is divided into two major parts: the neurohypophysis and the adenohypophysis.

The adenohypophysis or the anterior pituitary contains different cell types that produce six different protein hormones: growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin. FSH, LH and prolactine regulate the function of the ovaries and mammal glands. FSH and LH are synthesized and stored in cells called gonadotrophs. Prolactin is secreted by lactotrophs.

The target glands for the FSH and LH are the ovaries. So FSH stimulates growth and maturation of the follicle, proliferation of the granulesa-cells, induces the development of LH-receptors on the granulesa-cells surface. It also stimulates estradiol secretion . An increase in FSH level by a negative feedback mechanism is stimulated by the decreasing blood levels of estradiol and progesterone from the regressing corpus luteum.

LH stimulates the formation of androgens in teka-cells, along with the FSH it promotes ovulation and stimulates synthesis of progsterone by the luteinized granulesa cells of corpus luteum.

During the luteal phase, as a result of elevated circulating blood levels estradiol and progesterone , both LH and FSH are significantly supressed throught the negative feedback mechanism.

The fourth level of regulation of the menstrual cycle is the ovaries. Complex processes of steroidogenesis and development of the follicles take place here. Follicular development process in the ovaries occurs continuously. Primordial follicles consist of growing oocyte , zona pellucida and several layers of the follicular epithelium. Primordial follicles undergo sequential development, differentiation and maturation until the graafan follicle is produced. The follicle then ruptures with relasing of the egg and subsequent development of the corpus luteum.

During each cycle, a cohort of follicls undergo development. But only one usually continues differentiation and maturation into a follicle that ovulates.

Further growth of the follicle is due to the transformation of the follicular epithelium to multilayered, that produces follicular liquid (liquor folliculi), which contains the estrogens. The diameter of the mature follicle is about 18-25 mm. Maturation of the follicles depend on the development of FSH and LH receptors on granulesa- and theca-cells.

The levels of estrogens increase gradually during the first phase of the mestrual cycle from relatively low levels in the early follicular phase (60-100 mkg) to maximal level 1 day before the midcycle LH peak (400-900 mkg). The process of conversion of testosterone to estradiol in the granulesa cells of the follicle is called aromatization. It happens through the action of the enzyme aromatase. (Figure 4.1-3). Maternal substance for all steroid hormones is cholesterol.

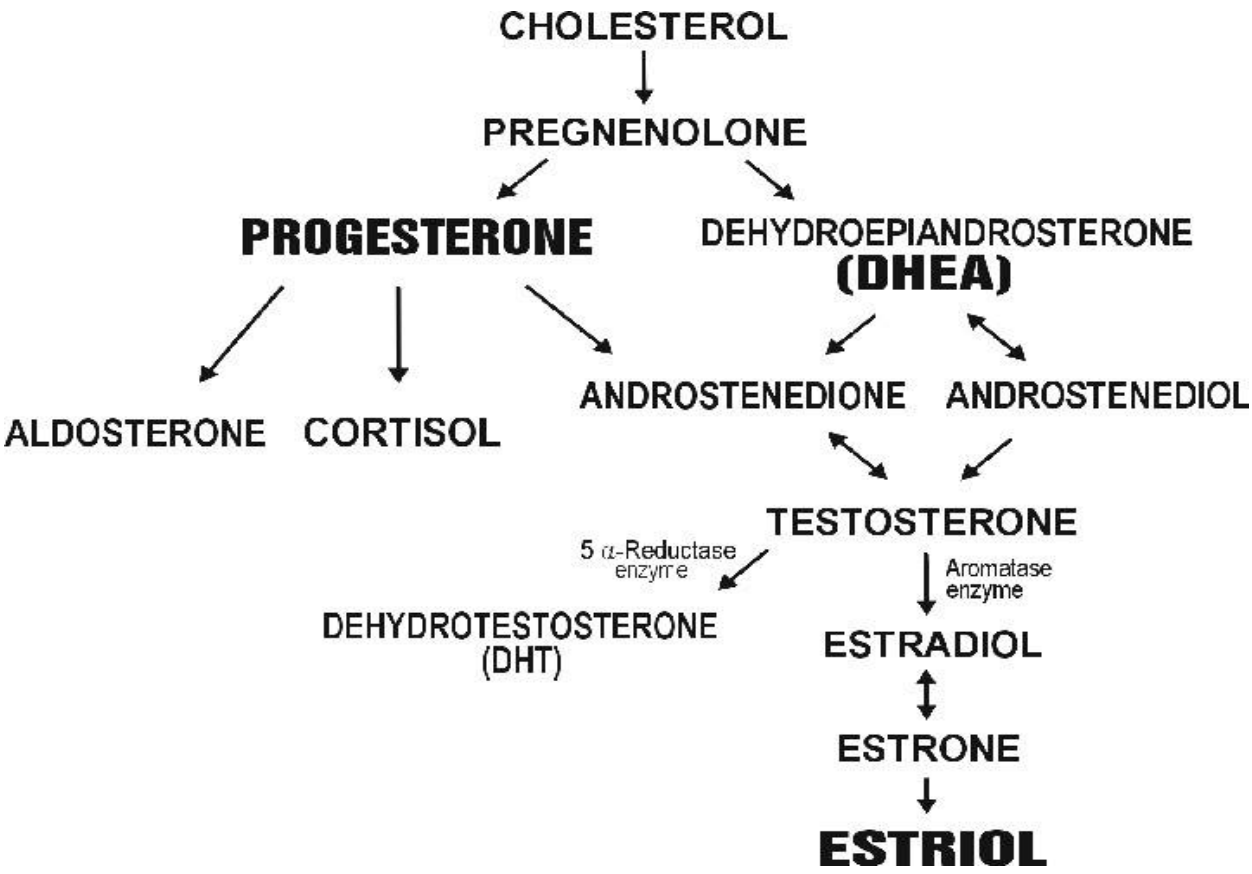


Figure 4.1-3 Diagrammatic representation of the steroid biosynthetic pathways

Just before the ovulation nonruptured but lutheinized follicle begins to produce progesterone. Only small amount of progesterone is produced by the ovaries. The bulk of the progesterone comes from the peripheral conversion of adrenal pregnenolone and pregnenolone sulfate. Corpus luteum is a main source for the progesterone during the second phase of the menstrual cycle and pregnancy. Secretion of the progesterone by the corpus luteum reaches it's maximal level 5-7 days after ovulation . Both easrogen and progesterone levels return to their baseline before menstruation.

The normal functional life span of the corpus luteum is about 9-10 days. In absence of pregnancy the corpus luteum is gradually replaces by the avascular scared tissue, called a corpus albicans.

The fifth level is the target organs, the point of application of the action of hormones. These include both the organs of the reproductive system- uterus, fallopian tubes and the vagina, and other organs: mammal glands, skin, bones and fat tissue. All of these organs containe receptors to the steroids.

The endometrium undergo changes during the whole menstrual cycle. It is responsive to the action of the circulating estrogens, progestines and androgens. The endometrium consists of two portions: outer portion , or functionalis, and inner portion, or basalis. Outer functional portion of the endometrium is exposed to the following changes, that can be divided into three phases: menstruation, regeneration and proliferation in the first phase , and secretion in the second phase of the menstrual cycle. Basal portion of the endometrium remains unchanged during each menstrual cycle and provides steam cells for the restoring of the functional portion.

Mentrual phase is characterized by the disruption and desintegration of the endometrial glands and stroma, leukocyte infiltration, and red blood cell extravasation. It is followed by menstrual bleeding.

Proliferative phase is characterized by the regeneration and proliferation of the endometrium functionalis due to estrogen stimulation. Series of changes occur in the epithelial lining, endometrial glands and connective tissue of the stroma. Proliferation of the endometrium reaches it maximum to the end of the first phase of the menstrual cycle.

Secretory phase is characterized by the secretion of the glycogen, mucus and other substances by the glands of endometrium as a response to the progesterone action. The functional layer of the endometrium becomes soft and it is ready for the implantation of the fertilized egg. If the pregnancy doesn’t occur, by the day 23, secretion of the progesterone and estradiol declines, and the endometrium undergoes involution with the subsequent menstrual bleeding.

So, reproductive system is a supersystem with a complex mechanism of regulation. The main points in the regulation of the function of the reproductive system are pulsatile secretion of the GnRH and regulation of FSH and LH secretion by the estradiol by the mechanism of positive and negative feedback.

4. 2 Premenstrual syndrome

Premenstrual syndrome –is a pathological complex of psychoemotional, behavioral and somatic symptoms manifested only in premenstrual days.Some patients also have a brief surge of symptoms at midsycle,the time of ovulation.

Symptoms appear

for 2-14 days before menstruation and dissapear immediately after the onset of menstruation or first 3-4 days of bleeding.

Incidence of PMS differ significantly and ranges from 20 to 80 %. Women with mild to moderate symptoms are said to have PMS, others with severe forms that interfere with normal daily functioning and relationship are said to have PMDD (premestrual dysphoric disorder). Frequency doesn’t depend on the ethnic and cultural characteristics,but more often urban dwellers and persons with chronic somatic disorders are susceptible to this syndrome. Peak frequency and severity of PMS manifestation is observed in reproductive ages (20-40 years)

The pathogenetic mechanism of PMS is very complex and still not well understood. There are several theories try to prove the development of this syndrome, but more reliable of them are hormonal and atypical metabolism of progesterone. Basis of hormonal theory is toxic influence of estradiol to central nervous system and progesterone insufficiency in the luteal phase of the menstrual cycle. So,abolition of the menstrual cycle with GnRH agonists, pregnancy,

postmenopause provides symptomatic relief, whereas sequential ovarian hormone therapy with estrogens and cycles with elevated luteal phase levels of estrogens are associated with severe symptoms of PMS. At the same time, clinical studies showed absence of difference in cyclic hormonal levels of steroids in patients with PMS and controls.

It was proved, that estrogens and progesterone have a significant impact on the CNS, regulation of reproductive function and limbic departments of the brain, which are responsible for the emotions and behavior. But this influence of hormones completely opposite. If estrogens have stimulating effect and positively affect mood, so progesterone, more precisely it's atypical metabolits, have anxietic effect, and in some cases may lead to development of major depressive episodes. So, allopregnenolone is a neuroactive progesterone metabolite that modulates central gamma-aminobutyric acid receptors, that modify behavior, emotion and response to stress.

Thus, in response to hormonal changes a violation of central neuroregulatory mechanisms , probably in women with genetic predisposition and adverse external influence may be considered the main pathogenetic mechanism of PMS and PMDD.

Recalling data of the Diagnistic and Statistical Manual of Mental Disorders, 4th ed. At least 5 of the 11 spesified symptoms must be present for the diagnosis of PMS or PMDD (Table 4.2-1)

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):

1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension, feelings of being “keyed up” or “on edge”
3. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
4. Persistent and marked anger or irritability or increased interpersonal conflicts
5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)

6. Subjective sense of difficulty in concentrating
7. Lethargy, easy fatigability, or marked lack of energy
8. Marked change in appetite, overeating, or specific food cravings
9. Hypersomnia or insomnia
10. A subjective sense of being overwhelmed or out of control
11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

Table 4.2-1 Research criteria for Premenstrual Dysphoric Disorder

These symptoms shoud be limited to the luteal phase only and should exclude preexisting depressive and personal disorders. It is important to make daily

registration of symptoms during at least two subsequent menstrual cycles. All the notes should be done by the patients daily before the bed time. Patients rate each symptome on a five –point scale, from zero (0) to four (4). The most common symptoms of PMS are: depressed mood, anxiety, irritability, fatique, bloating, weight gain, change of appetite, sleep disturbance, difficult concentration, reduced self-esteem, melancholy, feeling of hopelessness, headache, migraine, pain in muscles and joints.

There are the following variants of the PMS and PMDD:

I.symptoms appear during 1 week before the menstruation and resolve with the onset of menstruation

II.symptoms appear in preovulatory period and persist in the luteal phase

III.brief symptoms appear in the moment of ovulation and repeated in during the second week of the lutein phase

IV.symptoms appear in the moment of ovulation, persist during the whole lutein phase and next menstruation.There is only 5-10 days asymptomatic period during first phase of the menstrual cycle.

Treatment of PMS is pathogenetic. It includes psychotherpy, medicamentous, vitamine and hormonal therapy. Most women shoul be treated individually, depending on type and severity of the symptoms. For the treatment of such a symptoms like bloating and fliud retention administration of muld diuretics indicated. The mild anxiety may be treated by antianxiety agents, such as buspirone. One of the most effective methods of therapy for women with PMS is the selective serotonin reuptake inhibitors, such as fluoxetine, sertraline.

Hormonal treatment of PMS include administration of the combined oral contraceptives, progestines , espesially drosperinone, levonogestrel conteining intrauterine device “Mirena” and GnRH aginists for minimizing hot flashes. For reliefe of pain syndrome administration of NSAID indicated.

4.3 Amenorrhea and Oligomenorrhea

Amenorrhea is absence of menstruation during 6 month or more. Oligomenorrhea is infrequent menstruations when the interval between menstruations more than 35 days, and there are 4 to 9 episodes of menstruation during one year. Amenorrhea divided into primary and secondary.primary amenorrhea is absence of menarche, secondary amenorrhea is absence of menstruation 6 or more month after preexisting menstruations.

Etiology of amenorrhea mostly is failure of the secrotory activity of the ovaries, congenital abnormalities of the reproductive organs, chromosomal abnormalities.

Primary amenorrhea

Classified to true and false. False amenorrhea is amenorrhea, which happens due to congenital abnormalities of the female reproductive organs, such as entire hymen and atresia of the vagina or septate vagina.

True amenorrhea is the absense of menstruation by the age 16 due to hormonal insufficiency. There can be primary amenorrhea with secondary sexual characteristics and amenorrhea with no secondary sexual characteristics. Patients with primary amenorrhea without development of secondary sexual characteristics display the absence of the gonadal hormone secretion-hypogonadotropic hypogonadism ,or

inability of the ovaries to respond to the gonadotropic hormones-hypergonadotropic hypogonadism.

Etiologic factors for hypogonadotropic hypogonadism are lack in GnRH syntesis and release, mostly as a result of chromosomal abnormalities due to Kallmann syndrome, lesions of the hypothalamus and pituitary gland, including prolactin-secreting adenomas, craniopharyngioma, trauma, necrosis of the anterior pituitary or constitutionally delayed puberty. (Table 4.3-1). Main diagnostic criteria for the hypogonadotropic hypogonadism is low blood levels of FSH and clinical signs of absence of secondary sexual characteristics.

Hyperprolactinemia
Pituitary lesions (tumor, granuloma, abscess)
Cushing syndrome
Drug use (opiates, alcohol abuse)
Anabolic steroids use
Severe or chronic illness
Pituitary irradiation, trauma or surgery
Iron overload
Kallmann syndrome
Idiopathic hypogonadotropic hypogonadism
Other genetic mutations
Prader Willi syndrome

Table 4.3-1 Etiologies of Hypogonadotropic Hypogonadism. Modified from Darby E, Anawalt BD (2005)

Hypergonadotropic hypogonadism with sexual infantilism develops as a result of failure in gonadal development or premature gonadal failure. These patients may have pure gonadal agenesis or gonadal dysgenesis, abnormal development of gonads due to chromosomal abnormalities or

defect of estrogen and androgen production due to congenital ferment deficiency.

Turner syndrome (45XO), structurally abnormal X chromosome, mosaicism with or without Y chromosome, testicular regression syndrome, syndrom of ovarian resistance usually diagnosted in patients with hypergonadotropic hypogonadism. (Table 4.3-2) These patients have abnormal high blood levels of FSH, that is the main diagnostic criteria.

- **Pure Gonadal Dysgenesis**
  - **Phenotypically female with sexual infantilism,**
  - **primary amenorrhea,**
  - **normal stature,**
  - **no chromosomal abnormalities (46, XX or 46, XY)**
  - **Gonads**
    : usually streaks, some development of 2nd sexual characteristics

< Swyer syndrome >

- **mutations in the SRY (sex-determining region gene on the Y chromosome) located at Yp11 result in XY females with gonadal dysgenesis**
- **15~20% of women (46,XY)**

Table 4.3-2 Common chromosomal abnormalities causing Hypergonadotropic Hypogonadism

Treatment depends on the type of hypogonadism. Patients with Hypogonadotropic hypogonadism require pulsatile GnRH hormone administration by an infusion pump. After 6cycles of this therapy

incidence of pregnancy is about 70%. Patients with gonadal agenesis or dysgenesis require hormonal therapy with estrogens for the developing of secondary sexual characteristics. In some cases surgical operation is indicated because of the high risk of malignisation of the gonads. Using of in vitro fertilisation with donor oocytes is a method of choice in treatment of the patients with gonadal dysgenesis and 17-hydroxylase deficiency.

Amenorrgea with secondary sexual characteristics is a consequence of androgen insensitivity syndrome or testicular feminisation and agenesis or dysgenesis of the Mullerian duct. (Table 4.3-3)

	MRKH/MURCS	Isolated Vaginal Atresia	Androgen Insensitivity	WNT4 defect
Upper Vagina	no	various	no	no
Uterus	no	yes	no	no
Gonads	ovaries	ovaries	testis	Masculine ovary
Hyperandrogenism	no	no	no	yes
Breast enlargement	normal	normal	normal	normal
Karyotype	46 XX	46 XX	46 XX	46 XX
Pubic hair	normal	normal	rare	normal

Table 4.3-3 Main characteristics of the patients with Mayer-Rokitansky-Kuster-Hauser

Patients with testicular feminisation (46XY) have female appereance with vaginal dimple and no uterus, breast enlargement due to peripheric conversion of the androgens to estrogens, male levels of androgens because they have abdominally located testicles and elevated levels of FSH and LH.

Patients with agenesia or dysgenesia of mullerian duct have 46XX karyotype, normal female levels of testosterone and congenitally abnormal genitalia with agenesia and dysgenesia of the vagina, uterus, cervix and fallopian tubes. Most common pathology is Meyer-Rokitansky-Kustner-hauser syndrome. This syndrome is characterized by an isolated absence of the proximal two thirds of the vagina, unilateral or bilateral uterine tissue, fallopian tubes and normal functionating ovaries.

The differential diagnosis of amenorrhea with secondary sexual characteristics is based on the determination of androgen levels.

Treatment is surgical depending on the degree of dysgenesia.

Secondary amenorrhea

Secondary amenorrhea is distinguish to physiological and pathological. Physiological amenorrhea is assosiated with pregnancy, lactation and period of menopause. A variety of factors can contribute to pathological secondary amenorrhea:

- hormonal imbalance: tumors of pituitary gland, pathology of thyroid gland, low estrogen levels, high testosterone levels

-lifestyle factors: pure nutritient, emotional stress, excessive physical load, anorexia nevrosa

-yatrogenic factors: uterine instrumentation, curretage with following Asherman’s syndrome

-premature ovarian failure, caused by chromosomal disorders, injury from surgery, radiation, chemotherapy, galactosemia

-polycystic ovary syndrome

-adrenal disorders: congenital adrenal hyperplasia, Cushing's syndrome, adrenal neoplasms

Along with the missed periods 6 month and more, women with secondary amenorrhea also experience vaginal dryness, acne, headache, nipple discharge, deepening of the voice, abnormal facial and body hair growth, hot flashes, hair loss, significant weight change. (Table 4.3-4)

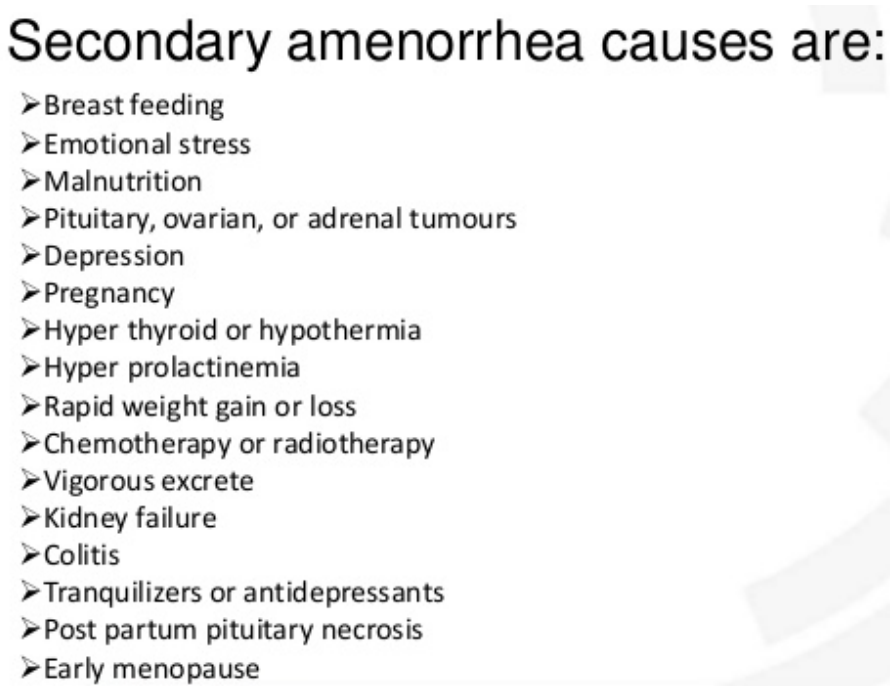


Table 4.3-4 Most common causes of secondary amenorrhea

Diagnosis of secondary amenorrhea is complex, including MRI and CT scans, US examination, determination of the blood hormone levels. (Table 4.3-5)

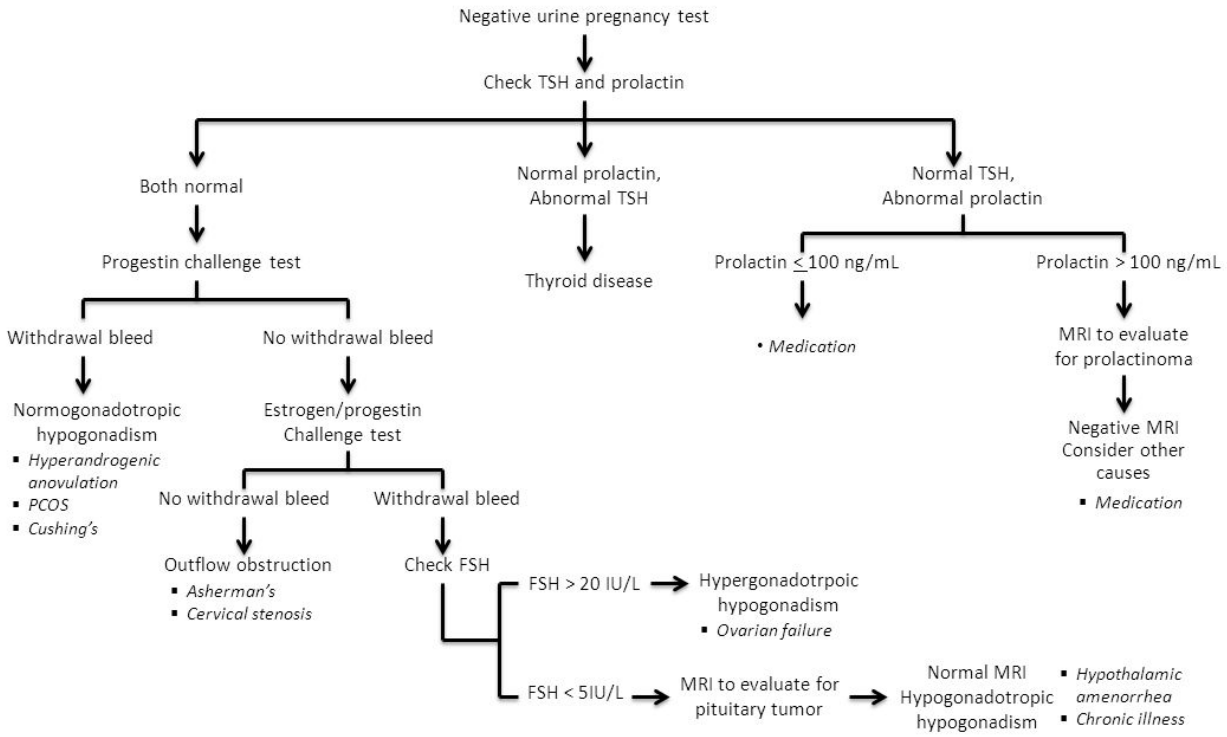


Table 4.3-5 Algorithm of evaluation of the patients with secondary amenorrhea

The treatment of the secondary amenorrhea varies depending on the underlying cause. Patients with premature ovarian failure and hormonal imbalance require hormonal therapy. Surgical treatment is indicated in case of tumors of pituitary gland and ovaries. Therapy with bromcriptine and cabergoline is administered for patients with hyperprolactinemia and galactorrhea. Also it is recommended to make certain lifestyle changes, improve nutrition, manage weight and physical activity in a healthy manner.

4.4 Polycystic Ovary Syndrome

PCOS at the present time is among the most serious and frequent patological conditions of modern reproductive medicine. 6 to 10% of

women of reproductive age have some form of PCOS, and, according to the some data, it is diagnosed in approximately 40% of infertile patients.

PCOS is a chronic condition with the clinical set of symptoms that characterized by oligo-, or amenorrhea and clinical and laboratory evidence of hyperandrogenism. It’s onset is coincide with the time of puberty. There is hereditary predisposition of PCOS in first-degree female reltives.

Most common signs of PCOS are: irregular menstrual periods (90%), infertility (75%), hirsutism (90%). Less common signs are: heavy periods, obesity, acne, pelvic pain, patches of dark velvety skin, hyperprolactinemia.

Pathophysiology of this disease is based on dysfunction of the hypothalamo-pituitary structures with changes in cyclic syntesis of gonadoliberines, gonadotropins and monoamines. These followed by increased LH pulse frequency, usually resulting in high circulating levels of LH. The increased LH level promotes androgen secretion from ovarian theka-cells, leading to elevated levels of ovarian-derived androstenedione and testosterone. Andrenal production of androgens also may incrase in patients with PCOS. Elevated levels of androgens affects the follicles and lead to their atresia and mid-antral stage arrest. There is no evidence of the dominant follicle.Peripheric conversion of androgens to estrogens, usually in the fat tissue, results in eleveted levels of estrogens more than in follicular phase that supress FSH release from the pituitary gland. These changes result anovulation. The unopposed

estrogen levels affect the endometrium and may lead to developmentof the endometrial hyperplasia and carcinoma.

Increased blood levels levels of free testosterone, as a result of decreasing production of SHBG (sexual hormone binding globuline) by the liver, is a result of hyperinsulinism and insulin resistance. About 70 % of patients with PCOS have signs of insuline resistance. This leads to developing of metabolic syndrome and obesity. (Table 4.4-1)

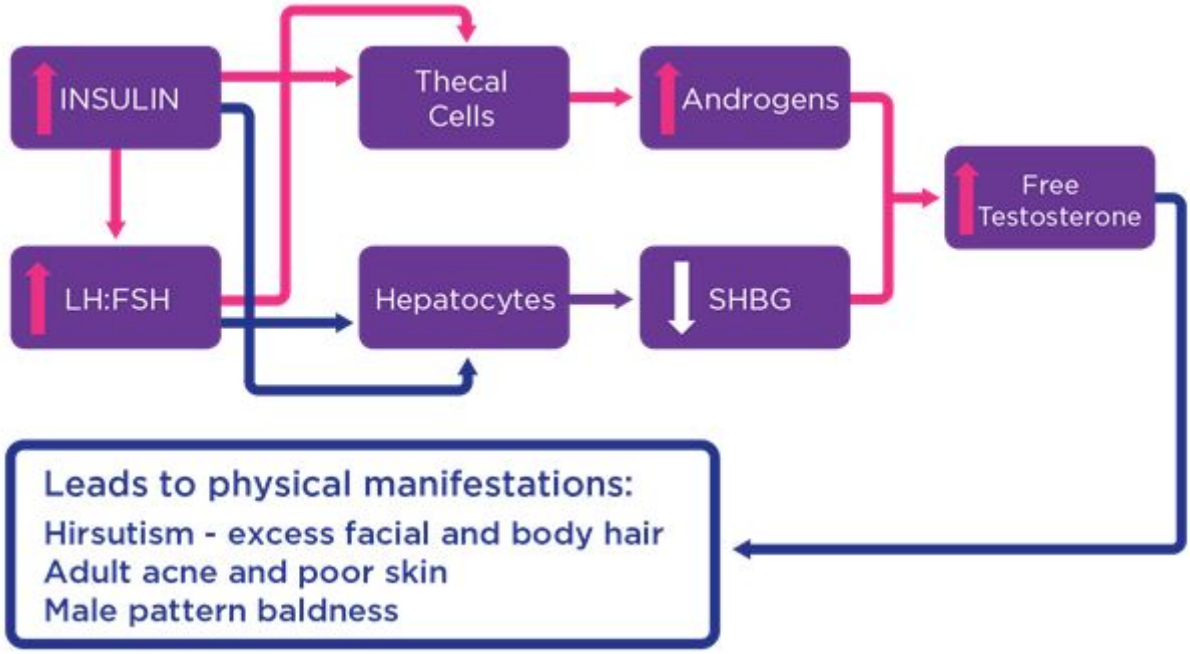


Table 4.4-1 Diagrammatic representation of the pathogenesis of PCOS

Diagnosis of PCOS is based on the laboratory findigs as determination of the hormone levels (LH, FSH, estradiol, progesterone, testosterone, prolactine, basal 17-hydroxyprogesterone, TSH, DHEA-S), LH/FSH relation, insuline. Ultrasound imaging demonstrates incresed ovarian volume with peripheric location of the follicles-pearl necklace sign, hyperplasia of the endometrium. Bimanual examination may identify

ovarian enlargement. (Figure 4.4-1)

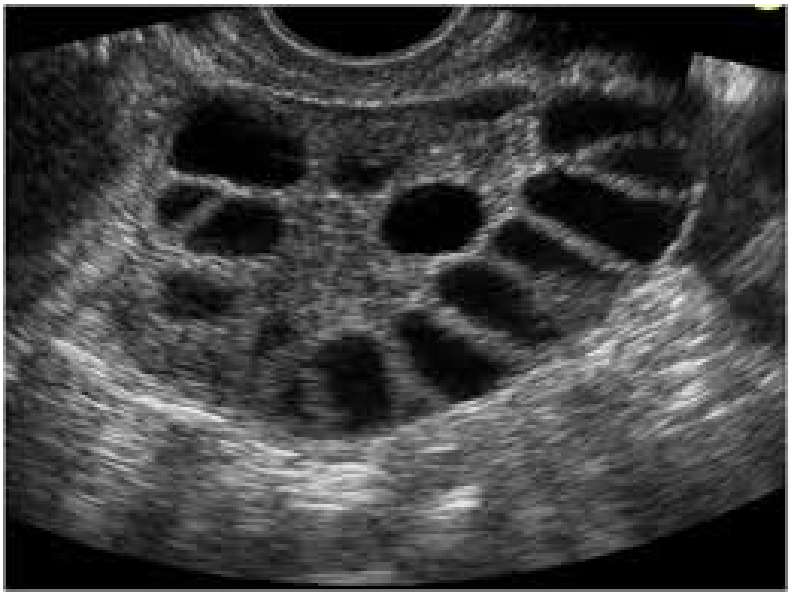


Figure 4.4-1 Ultrasound image of ovary with PCOS, sign of “Pearl necklace”

Treatment of the PCOS is directed to the elimination of the insulin resistance, normalisation of body weight, treatment of hirsutism and acne by administration of combined oral contraceptives and androgen receptors blockers. In case of infertility stimulation of ovulation is indicated.

Physical examination includes determination of the degree of hirsutism, presence of acne, allopecia, dark velvety skin patches.

Chapter review

1. What amenorrhea is:

A) Absence of menstruation more than 6 month

B) Absence of mnstruation more than 2 month

C) Absence of menstruation more than 4 month

D) Excessive menstrual bleeding

E) Excessive acyclic bleeding

2. Psysiologic amenorrhea is not evident in:

A) Reproductive period

B) Before puberty

C) During lactation

D) During pregnancy

E) In postmenopause

3. Where does the prolactine syntesis take place?

A) In pituitary gland

B) In thyroid gland

C) In ovaries

D) In adrenal gland

E) In hypothalamus

4. It’s not characteristic for PCOS:

A) Pathologic high levels of prolactine

B) Increasing of ovarean capasity

C) Hirsutism

D) Obesity

E) Amenorrhea

5. Which medicine is indicated for the treatment of hyperprolactinemia?

A) Bromcryptine or cabergoline

B) Busereline

C) Chorionic gonadotropine

D) Combined oral contraceptives

E) Progestagens

6. The duration of normal menstrual cycle is:

A) 21-35 days

B) 28-40 days

C) 3-7 days

D) 28-29 days

E) 14-28 days

7. The main criteria for two phased menstrual cycle is:

A) Ovulation

B) Onset of menarche

C) Prolifiration of the endometrium

D) Elevated levels of androgens

E) Menorrhagia

8. Pseudoamenorrhea is evident at:

A) Atresia of cervical canal

B) Aplasia of the uterus

C) Dysgenesia of gonads

D) Anorexia nevrosa

E) Coushing’s disease

9. Which pathologic condition in teenagers followed by amenorrhea requires urgent surgical intervention?

A) Entire hymen

B) Meyer-Rokitansky-Kustner syndrome

C) Hyperprolactinemia

D) Syndrome of testicular feminisation

E) Turner’s syndrome

10. Which structure is responcible for GnRH syntesis?

A) Hypothalamic nuclei

B) Corpus luteum

C) Adrenal gland

D) Thyroid gland

E) Pituitary gland

Chapter 5.Genital Tract Infections and Pelvic Inflammatory Disease

5.1 Physiology of the vagina

The vagina is muscular organ and situated between the cervix and the vulva. The vagina has two main functions: sexual intercourse and childbirth. The human vagina is lined by nonkeratinized stratified squamous epithelium, which has no glands. It’s physiology is influenced by the hormones: estrogens and progesterone.

Normal enviroment of the vagina is a unique balanced ecosystem. The microflora of the vagina is a natural protection of female reproductive organs from the patogenic microorganisms. There are some factors that help to support normal microflora of the vagina. They are anatomical and functional. Anatomical factors are: closed vaginal opening, pubic and perineal hairs, cervix. Functional factors are: vaginal transudate, Ph

of the vagina equal to 4-4.5 and monthly cleansing of the vagina by menstrual bleeding.

As baby-girl passed through the birth canal, it’s vagina is colonized by aerobic and anaerobic bacteria. Due to rich estrogenization of the vagina of the newborn, pH becomes to decrease and lactobacilli start to growth. This fenomena increases the protective ability of the vagina. Within days after birth, level of estrogens decreases and it leads to rising of the pH and lactobacilli are replaced by gram-positive cocci and bacilli.

With the onset of pubety and ovarian steroidogenesis, the vaginal flora changes and is presented mostly by lactic-acid and peroxide-producing lactobacilli.The pH of the vagina is 3.5-4.5. Lactobacilli are most prevalent, but many other facultative and anaerobic microorganisms are present. (Table 5.1-1) Aerobic bacteria decrease premenstrually wheres anaerobes remain in constant level.

Microscopic Picture	I	II	III	IV
Lactobacillus	+++	++	+	-
Comma variabile	-	-	++	++
Gram negative cocci	-	-	++	++
Anaerobic, streptococcus, Trichomonas vaginalis	-	-	+/-	+++
Leucocytes	-	+	++	+++
Epithelial cells	-	+	+	++

Table 5.1-1 Evaluation of vaginal smear. Degrees of purity of the vagina

Major components of the vaginal secretion are transudating through the vaginal walls. With desquamated epithelial cells, cervical mucous, fluids from the upper genital tract, exudates from the Bartolin's and Skene's glands, leucocytes and metabolic products of the vaginal microflora. Vaginal fluid is composed of proteins, carbohydrates, fatty acides, enzymes and immunoglobulines. Estrogenes and sexual intercourse increase amount of vaginal fluid. Decreasing of the estrogens, especially in postmenopause markedly decrease vaginal fluid.

A lot of factors may affect the normal microflora of the vagina and decrease it protective ability: antibiotics, pregnancy, sexual intercourse, excessive douching, chemotherapy, anemia, severe chronic extragenital diseases. Disturbances in the vaginal ecosystem may have a potential impact on many diseases, and thus deserve careful studies.

5.2 Vulvovaginitis

In the structure of the diseases of female reproductive organs inflammatory diseases have a leading point (60-65%). Vulvovaginitis is the one of the most common complaines of the gynecologic patients. But there are difficulties in the exact data because of high incidence of self-treatment and asymptomatic duration of the disease.

Vaginitis is the inflammation of the lining of the vagina. It may be due to an infection, allergic reaction, or dryness as a result of low estrogen

levels, generally in postmenopause (atrophic vaginitis). It often follows with the inflammation of the vulva.

Depending on the nature of the pathogen all the vulvovaginitis are divided into specific and nonspecific. Etiologic agents for nonspecific vulvovaginitis are staphylococcus, streptococcus, Escherichia coli and other microb associations. Specific vulvovaginites are caused by exact pathogenic agent, most common are Neisseria gonorrhoea, Candida, Trichomonada vaginalis, mycoplasma, chlamidia or BV associated bacteria.

In some cases vulvovaginates occure without any pathogens. These are so-called noninfectious vulvovaginitis. They develop as e result of allergic, mechanical, chemical and thermal exposure.

Up to 90% of cases of vaginitis appear to be caused by three conditions. Bacterial vaginosis accounts for 40% to 50%, vulvuvaginal candidiasis for 20% to 25%, and trichomoniasis for 15% of cases.

Bacterial vaginosis

There is a high incidence of BV in women of early reproductive age with excessive vaginal discharge (61%). According to data, 24% of practically healthy women without any complaines were demonstrated BV in a routine gynecological examination. BV is associated by disturbances in normal vaginal ecosystem, with replacement of lactobacilli by other microbs, predominantely by BV-complex microorganisms: Gardnerella vaginalis, genital mycoplasmas, and anaerobic bacteria, including Prevotella, Bacteroides, Mobilincus.

Studies proved that BV is a risk factor for severe patological conditions of reproductive organs and complications of pregnancy. It is one of the causes for premature labor.

There is no evidence of contamination with BV from sexual partner. But it detected among women with several sexual partners, smoking, using intrauterine device.

There are two types of clinical manifestation of the BV: asymptomatic and with clinical symptoms. Asymptomatic patients present laboratory findigs of BV without any clinical symptom.

Classic symptoms of BV include a profuse, milky, nonadherent white to grayish discharge with spesific odor of spoiled fish, associated with frequent pathological processes of the cervix and recurrent duration.

Main diagnostic criteria for BV along with clinical findings, are laboratory tests: determination of the clue cells in a saline wet-mount preparation, and testing for the present of an amine odor by puting few drops of 10% potassium hydroxide (KOH) in the vaginal discharge. Clue cells are mature epithelial cells surrounded by adherent microorganisms, associated with BV. pH of the vagina in patients with BV is more than 4.5. (Figure 5.2-1)

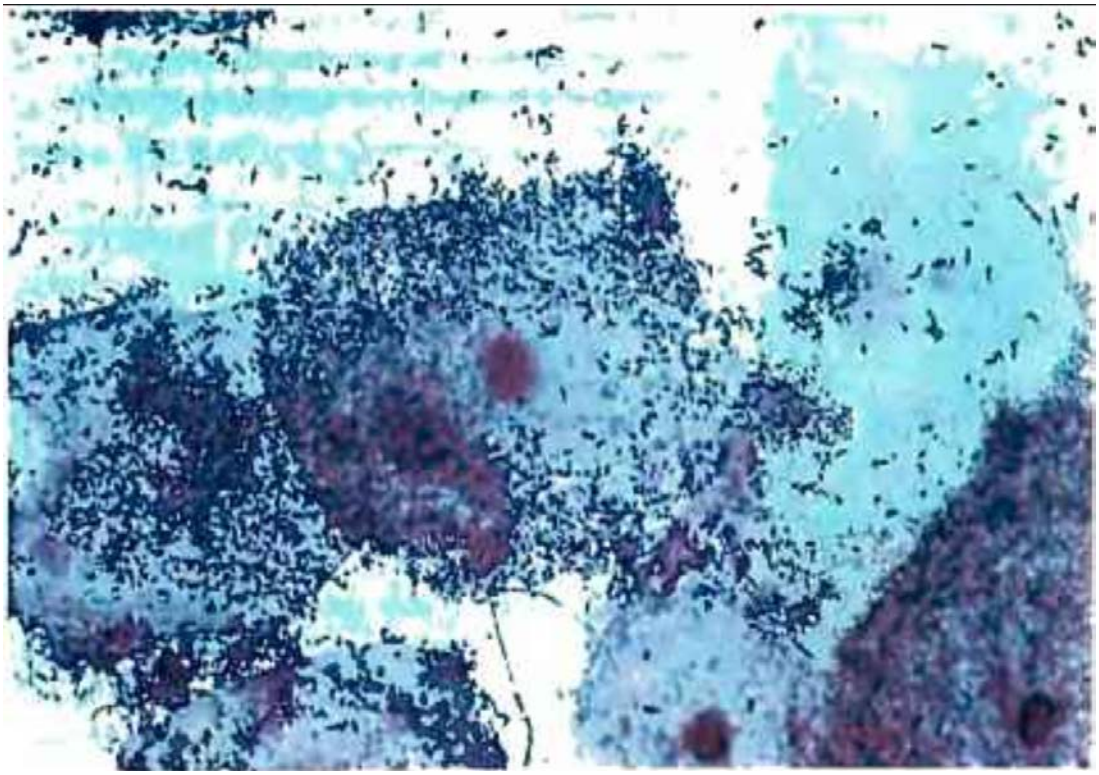


Figure 5.1-1 Microscopic view of clue cells

First-line treatments for BV include metronidazole and clyndamicine. Partner treatment is generally not recommended.

Vulvovaginal candidiasis

The incidence of vulvovaginal candidiasis continues to increase. And it is the second common cause of specific vulvovaginitis. Etiologic agents of VVC are Candida albicans – in 90% and Candida glabrata –in 15% of cases.

Candidas are type of yeasts. They are conditionally-pathogenic, aerobic microorganisms. The optimal pH for the growth of the candida is 6.0-

6.5. Usually Candida affect women in reproductive age, because of it’s requirement for estrogens.

Predispositing factors for developing of VVC are: pregnancy, antibiotic therapy, combined oral contraceptives, diabetus mellitus, tight occlusive clothing, chemotherapy and immunosupression.

About 75% of women acquire VVC at some time in their life, and 5% suffer frequent symptomatic recurrences. If at least four episodes of VVC occure within 1 year, it considered recurrent.

There are three clinical types of VVC:

-latent candidiasis

-acute genital candidiasis

-chronic (recurrent) candidiasis

Patients with latent candidiasis have no clinical symptoms, but have laboratory findings. In certain conditions it may develops to clinically active form.

Acute candidiasis has significant manifestation of the clinical symptoms such as vaginal itching, irritation, burning, erythema of the vulva and disuria. The discharge is odorless, thick or curdy with the appearance of

cottage cheese. (Figure 5.2-2)

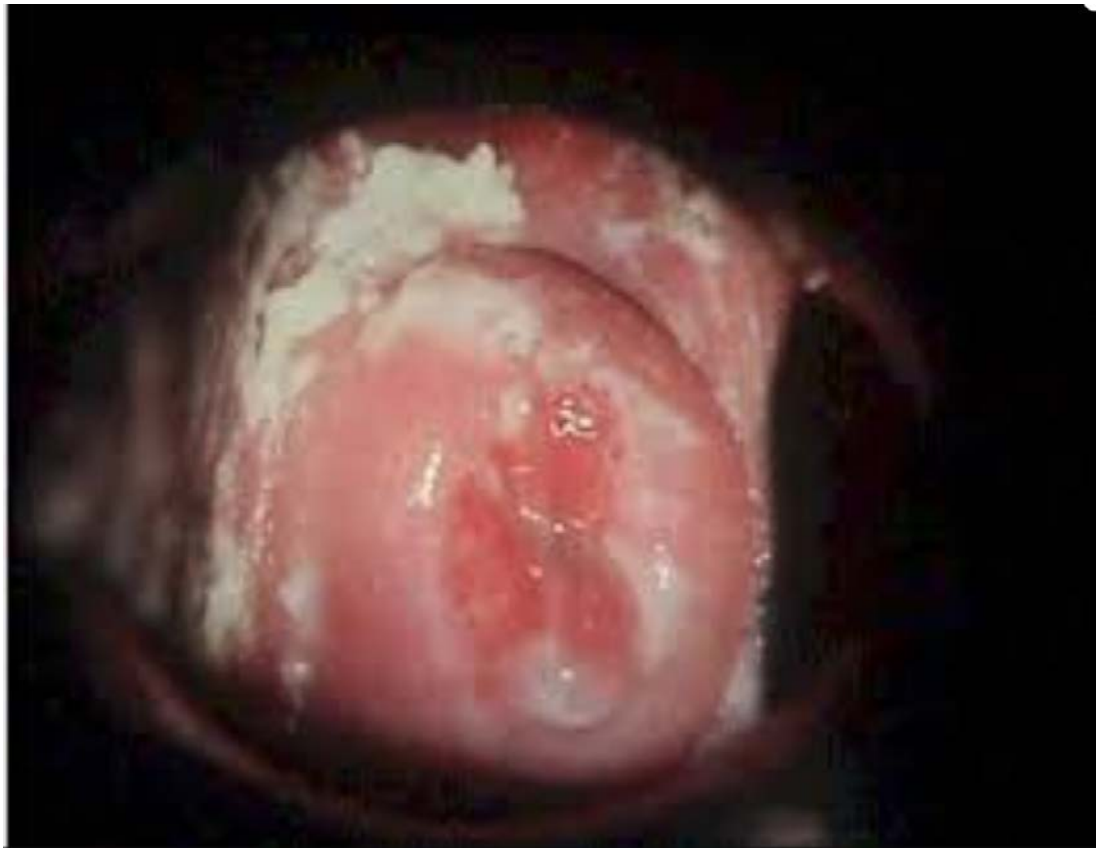


Figure 5.2-2 Cottage cheese or curd-like appearance of vaginal discharge

Chronic or recurrent type of VVC is most common. There are two main causes for developing of recurrent VVC: reinfection and insufficient elimination of the pathogen. Self diagnosed and treatet cases of VVC decrease a frequency of doctor visit, and, thereby contribute the transition of the disease to the chronic form.

Diagnosis of VVC is based on clinical manifestation of the disease and laboratory findings of budding yeast cells, pseudohyphae or mycelial tangles in a wet-mount preparation.

Treatment includes oral antifungal agents (imidazole, fluconazole, itraconazole, klotrimazole, natamicine) and vaginal applications of antifungal creams and suppositories. VVC is not sexually transmitted infection, but due to high incidence of reinfection sexual partners sometimes require routine treatment.

Trichomoniasis

Trichomoniasis is one of the common sexually transmitted diseases that is caused by a protozoan parasite called Trichomonas vaginalis. The source of the disease is infected person with clinical manifestation of the disease or with asymptomatic trichomoniasis. Occasionally infection may transit through contaminated personal hygiene items and medical instruments. The incidence of trichomoniasis is equal in males and females, but in males duration of the disease is usually asymptomatic, or has signs of nongonococcal uretritis at direct examination. About 50% of contaminated women are olso asymptomatic.

There are three types of trichomoniasis: vaginal, rectal and oral. Symptomes of the disease may vary from mild irritation to severe inflammation with damaging of upper reproductive organs. The incubation period of the disease is approximately 5-28 days after being infected. Clinical symptoms of the trichomoniasis are typical:

-excessive yellow-green frothy or liquid discharge without or with musty odor

-itching, burning of the vulva

-disuria

-mild vaginal bloody spotting

-dispareunia

-lower back pain

One of the specific symptoms of the trichomoniasis is affection of the cervix, so called “strawberry” cervix due to capillary dilatation as a result of the inflammatory response.

Diagnosis is usually made on clinical grounds and laboratory examinations, including bacterioscopy-determination of the characteristic motility of the trichomonads on a saline wet-mount preparation: polymerase chain reaction, and antigen testing. (Figure 5.2-3)

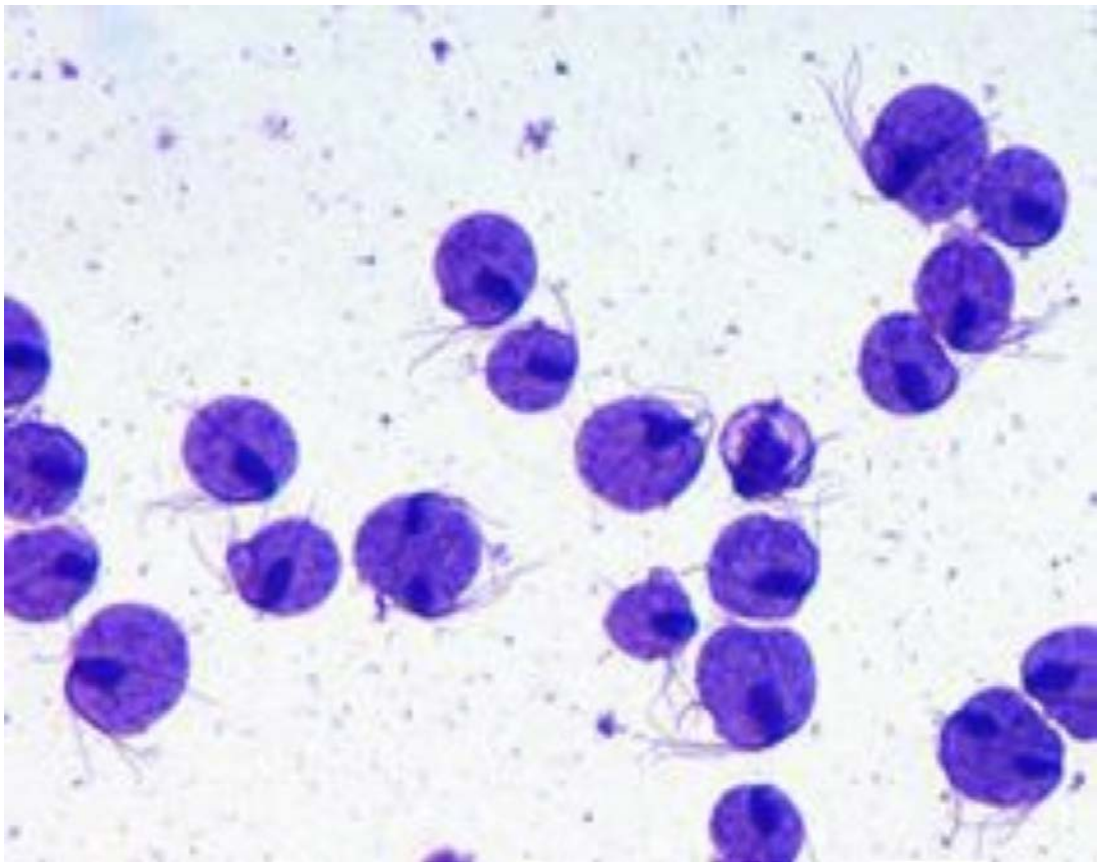


Figure 5.2-3 Microscopic view of trichomonad in a saline wet-mount preparation

Treatment of trichomoniasis is administration of single oral dose (2g) of metronidazole. In patients with resistance to metronidazole, treatment with tinidazole or higher doses of metronidazole (2g daily during 7 days) is indicated. Patients during treatment should avoid sexual contact and alcohol consume. Treatment of the sexual partner is necessary.

Atrophic vaginitis

It is a most common condition observed in a climacteric women. Atrophic vaginitis is nonspecific irritation and thinning of the vaginal mucosa, which followed by dryness, itching and purulent to yellow discharge. The main cause is deficiency of the estrogens .

That leads to thinning of the vagial mucosa because of the poor blood supply and dryness, increasing of pH, predisposing to activisation of the saprophytic flora of the vagina.

Clinical manifestations of the disease are: vaginal itching and discomfort, burning at the urination, dispareunia, periodic bloody discharge.

Diagnosis is confirmed by routine ginecological examination with speculum, preparation of Papanicolaou smear with determination of the

immature basal cells and parabasal cells replacing superficial vaginal epithelial cells, colposcopy, pH determination.

The treatment of choice is administration of the replacing hormonal therapy and vaginal administration of estrogen containing creams, suppositories, or rings.

5.3 Sexually Transmitted Infection

The infections described in this chapter are passed from one person to another through the sexual contact. The incidence of STI is increasing annually. It’s associated with the early onset of sexual life, numerous sexual partners, disregarding in using of barier contraceptives, self treatment, problems of sexual behavior. The person with an STI may be infected and infect others without actually “having a disease”. It is a social-economic problem that requires detailed investigations and groundworks for cure and prevention of disorders caused by STI’s. The most common STI’s are chlamydia, genital herpes, gonorrhea, and human papillomavirus. (Figure 5.3-1)

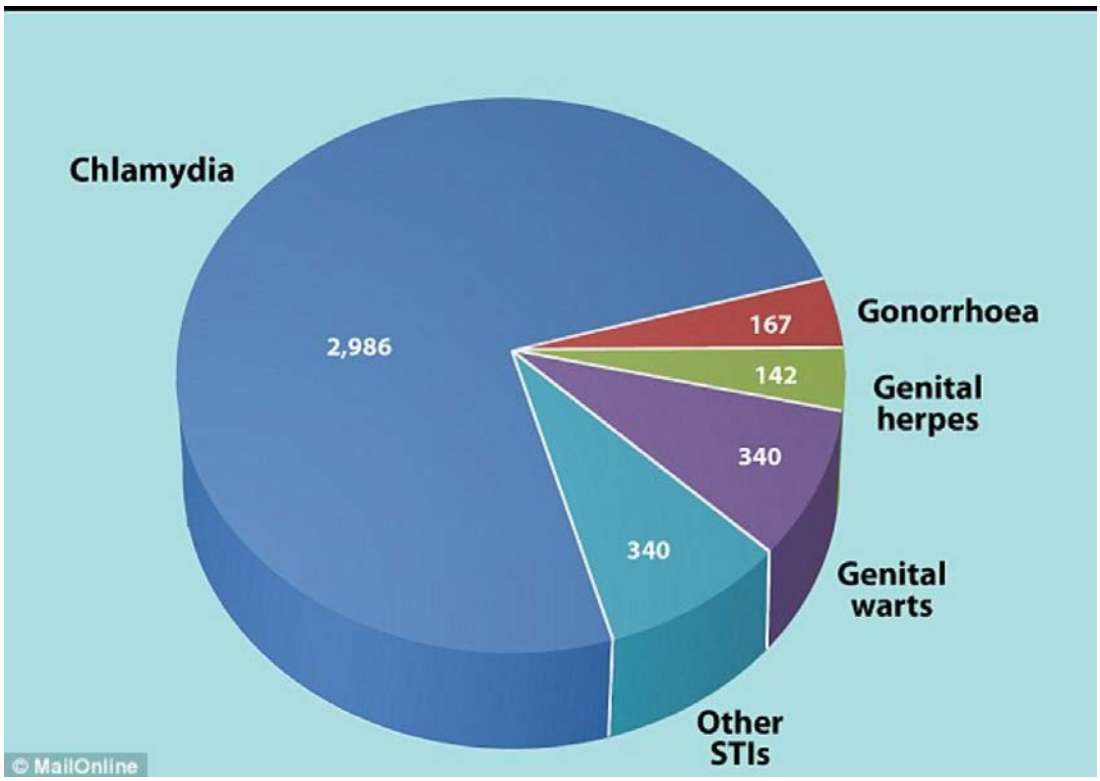


Figure 5.3-1 Diagrammatic representation of the incidence of the most common STI's

Chlamydia

Chlamydia is sexually trensmitted urogenital infection. The incidence of chlamydia is very high, in Unated States 4-5%, in Azerbaijan is about 12-15%. Pathogenic agent of the disease is Chlamidia trachomatis, an obligate intracellular bacteria. It has characteristic properties of viruses and bacteria, and, thus, difficult to treat. Chlamidia infects columnar epithelium of the cervix, endometrium, fallopean tubes, urethra and the rectum. This organism can persist for long periods in an asymptomatic carrier state. 70% of women and 50% of men have asymptomatic duration of the disease.

Chlamidia is one of the causes of infertility and ectopic pregnancy due to inflammatory processes of upper female reproductive organs. It also comlicates pregnancy with premature delivery (13%) and spontaneous abortion (11%).

There are two biological forms of chlamidia: elementary and reticular bodies. Elementary body is a high virulent form of pathogen, adapted to extracellular survival. Reticular body is an intracellular metabolic active form of pathogen, ensuring reproduction of the microorganism. People of any age can get infected by chlamydia, but most cases are found in patients younger than 25 years.

The clinical manifestations of genital chlamidya are mucopurulent cervicitis, disuria, dispareunia, abnormal vaginal discharge, bloody spotting, usually after sexual intercourse due to swollen friable cervix, itching and burning in or around vaginal opening.

Diagnosis of chlamydia is confirmed by various laboratory tests: detection of chlamydia antigens in a primary material by the methods of immunofluorescence and immunoferment analisys: tissue culture: DNA hybridization test and PCR (polymerase chain reaction). Each of these methods has it’s own advantages and disadvantages, so it’s better to use combination of them.

Selective screening should be performed at least annually on all sexually active females younger than 26 and all women with risk factors.

General treatment guidlines for lower genital tract infections include the following:

-presumtive treatment with antibiotics

-treatment of the sexual partners,that have sexual contacts within the past 60 days before diagnosis

-testing for other STI

-abstinence from sexual contact until patients and their sexual partners have completed tratment, or wait 7 days if treated with Azytromycin.

Treatment by antibiotics includes

-recommended regimens: Doxycycline 100 mg bd for 7 days, or Azithromycin 1mg orally in a single dose

-alternative regimen: Erythromycin 500 mg bd for 10-14 days, or Ofloxacin 200 mg bd or 400 mg once a day for 7 days

A test of cure is not routinely recommended but should be performed in pregnancy or re-exposure is suspected. It should be deferred for 5 weeks after treatment is completed.

Gonorrhea

It is sexually transmitted infection caused by Neisseria gonorrhoae. Incidence of gonorrhea is very high, there are as many as 700000 new cases of gonorrhea in United States. Affects selectively columnar epithelium, and, accordingly causes inflammation of the urethra, Bartoline’s gland, endocervix, uterus, fallopian tubes and pelvic peritoneum. Infection occurs mainly through sexual contact, but also

through contaminated items of personal hygiene. Contamination of newborn is possible passing through the birth canal. There is no vaccination and no immunity, that’s why there is possibility to get sick several times throughout the life.

There are acute and chronic forms of gonorrhea.

Most infected women have no symptoms due to anatomical structure of the urogenital organs. When symptoms do occur, they are often within 2 to 10 days after exposure, but they can take up to 30 days to develop. And first symptoms of the disease are itching of the urethra, painful and more frequent urination. Clinical manifestation of gonorrhea include:

-greenish-yellow discharge from the vagina

-lower abdominal or pelvic pain

-bleeding between periods

-swelling of the vulva

-spotting after intercourse

-conjuctivitis

-burning in the throat

Chronic gonorrhea is a latent form of disease lasting more than 2 month. Asymptomatic women usually continue to have sexual contacts and thus contributing to the spread of infection. About 15% of untreated gonococcal cervical infections progress to PID.

Diagnosis of gonorrhea includes Gram stain of the vaginal or cervical discharge, Thayer-martin or Transgrow media culture, DNA hybridization test and PCR and ligase chain reaction. These test can be done on urine or cervicl swabs. (Figure 5.3-2)

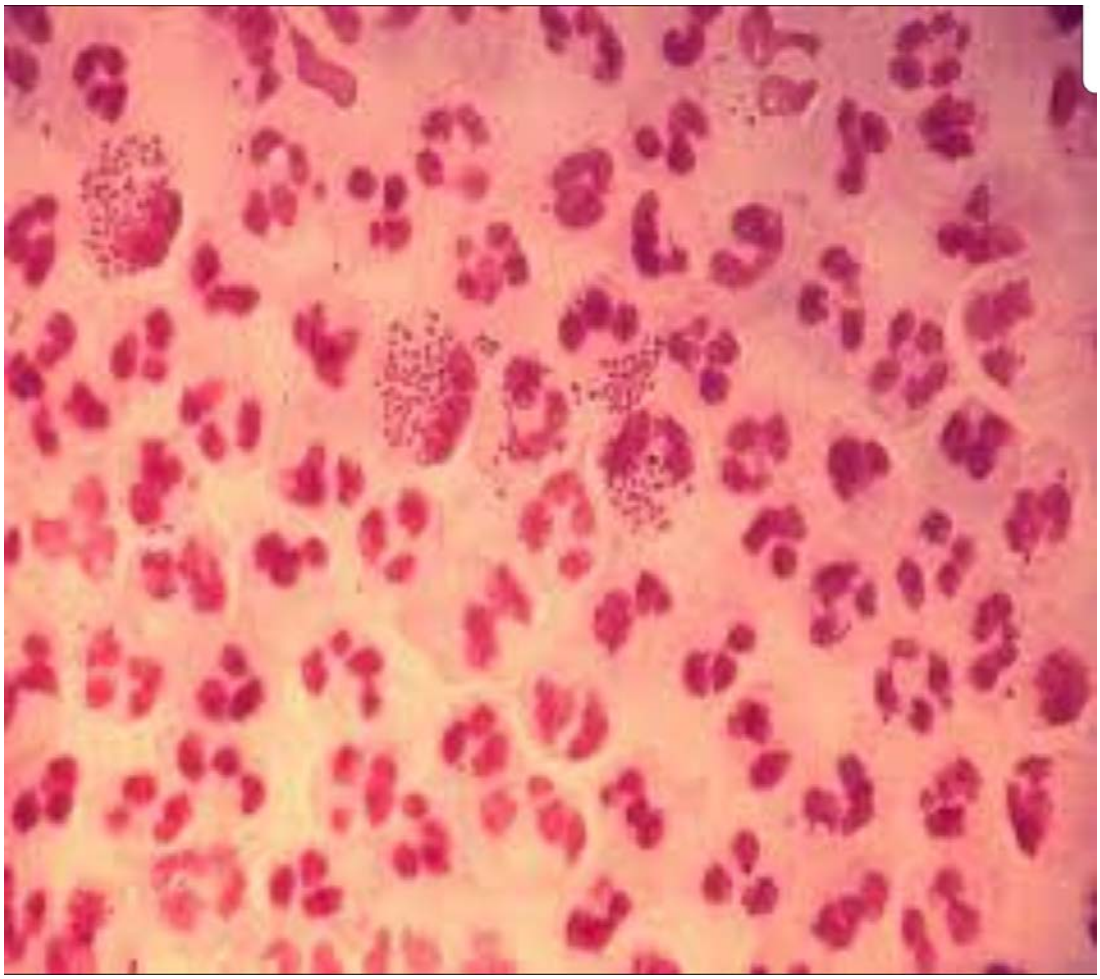


Figure 5.3-2 Microscopic view of gram-negative diplococci

Since 2010, CDC (Centers of Disease Control and Prevention) has recommended dual therapy to treat gonorrhea that includes a cephalosporin-either the oral antibiotic cefixime or the injectable antibiotic ceftriaxon.

For patients with uncomplicated genital, rectal, or pharyngeal gonorrhea, CDC not recommends therapy with ceftriaxone, 250 mg as a single intramuscular dose, plus either azythromycin, 1 g orally in a single dose, or doxycycline, 100 mg orally twice daily for 7 days.

Rescreening of the patient to check up for infection should be done in 2 to 3 months, so doing 2-3 combined provocations and Gram stain of the discharge during each menstruation.

Genital Herpes

At the present there is a significant increasing incidence of herpetic infection all over the world. A new study of the WHO shows that two thirdsof people –or 3.7 billion-under age 50 are infected with the herpes simplex virus type 1, and about 1.5 million new cases occuring every year. Genital herper may be caused by either herpes simplex virus! (HSV-1) or type 2 (HSV-2), but globally ,the large majority of cases are caused by HSV-2. Herpetic infection has great ability to a non-replicating state known as latency.That's why, only 10% to 20% of infected person know that they are infected. Periodic reactivation from latency is possible and leads to viral shedding from the site of the initial infection.

HSV-1 most commonly causes skin lesions, or cold sores around the mouth, but latest researches show that it also can cause genital lesions as well. The virus enters the body through mucosa or microabrasions of the skin and follows the sensory nervs to the dorsal spinal ganglion, where it

remains latent until reactivated. Was proved that 65% of persons with genital herpes are contagious during 1-7 days of conditional remission, so that in 30% of cases asymptomatic expression of the virus occurs 7 days befor the apearance of the lesions, and in 20% of cases within 7 days of the recurrence. The incidence of asymtomatic transmission of the infection increases in those with high frequency of the recurrencies.

Recurrent genital herpes infection occurs when the infected person has HSV antibodiesto the same serotype. In this case the lesions are fewer, unilateral, and less painful.

First attack of the genital herpes include following symptoms:

-fever anf flu-like symptoms

-muscle aches

-disuria

-burning and itching in the area of lesions

-multiple painful anogenital vesicles or ulcers with an erythematous base

-regional lymphadenopathy

The lesions heal without scarring in 14-20 days. (Figure 5.3-3)

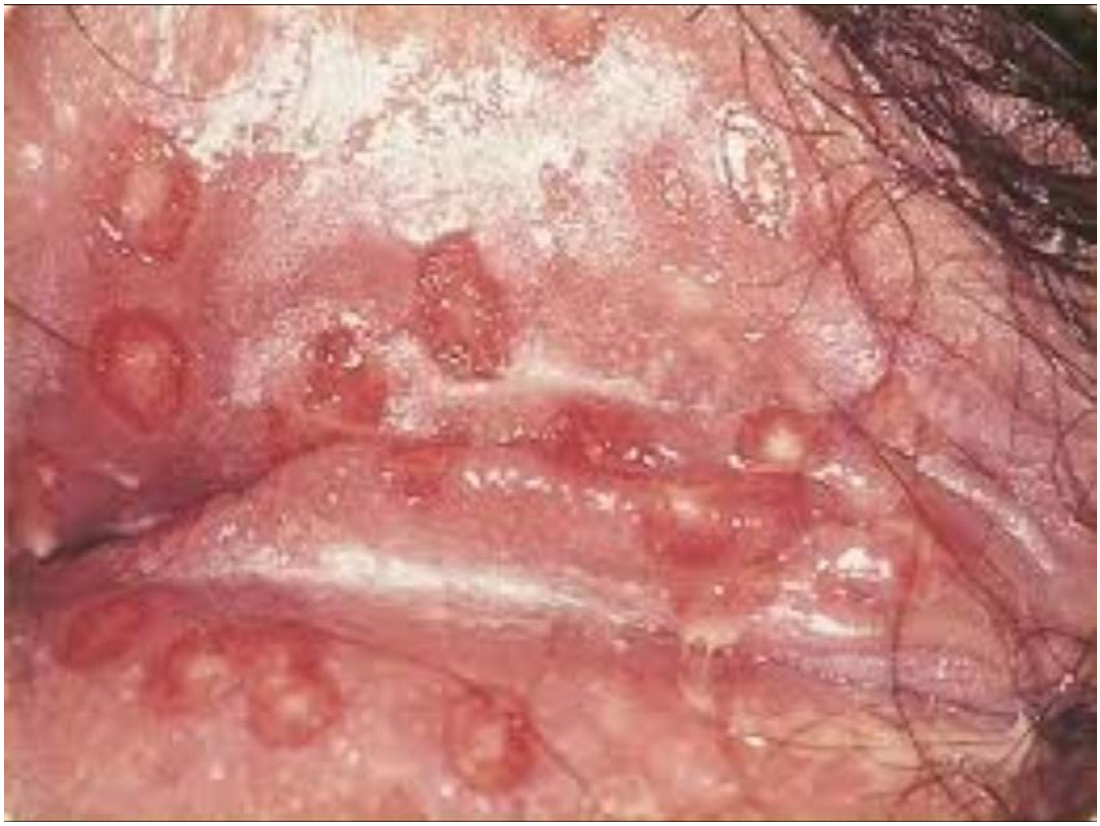


Figure 5.3-3 Herpetic lesions of the vulva

Diagnosis of genital herpes is based on clinical symptoms and laboratory findings. Laboratory tests include: type-spesific serologic tests for determinatio of the HSV-1 and HSV-2 antibodies;viral culture; PCR

Treatment of the genital herpes include antiviral agents (acyclovir, famcyclovir, valacyclovir), interferones, immunomodulators, local application of the antiviral creams. Therapeutic dose of the acyclovir is 200 mg 5 time per day during 5 days, of valtrex 500 mg once a day during 5 days.

Treatment for genital herpes is directed to symptom relief, acceleration of lesion healing, and decrease the frequency of the recurrencies. There is no complete elimination of the virus from the organism.

Human Papillomavarus

HPV is one of the most common STI and the only cause for cervical cancer, which is the second most common cancer in women worldwide. About 70% of sexually active men and women acquire genital HPV infection at some point of their life. Studies show that about 10 to 30 identified genital HPV types can lead to development of cervical cancer.

There are more than 200 subtypes of HPV. More than 30 of these viruses are sexually transmitted. HPV is spread through direct sexual contact, or skin-to-skin contact during sexual acts. All HPV types are epitheliotropic, and fully differenciated squamous epithelium is required for completion of the HPV life cycle. HPV infects keratinocytes, the predominant cell of epithelial surface. HPV is transmitted by contact with desquamated kerotinocytes from an infected person.

In most of the cases the individuals infected by HPV are asymptomatic. The most common sign of the HPV is genital warts, so called condylomas. They usually occur in anogenital area and vary in size and shape. Most common type is condyloma acuminata, that locates on the vulva, vagina, cervix, urethra, and perianal area. Subclinical types associated with precancerous and cancerous changes of the cervic, that diagnosed only during colposcopy. (Table 5.3-1)

Pap smear result	Management
Unsatisfactory	Repeat Pap smear
Severe inflammation	Evaluate for infection; repeat Pap smear if inadequate
ASC-US ASC-H	Colposcopy, biopsy if indicated; endocervical sampling if unsatisfactory colposcopy; follow with Pap smear every 6 months, consider repeat colposcopy annually if Pap smear unchanged
LGSIL, CIN 1	Colposcopy, biopsy if indicated; endocervical sampling if unsatisfactory colposcopy; follow with Pap smear every 6 months, consider repeat colposcopy annually if Pap smear unchanged
HGSIL, CIN 2 to 3	Colposcopy, biopsy +/- endocervical sampling; treat with loop excision or conisation
Atypical glandular cells AGC	Colposcopy, endocervical sampling; endometrial sampling if >35 years or with abnormal bleeding; cervical conisation if initial evaluation negative and cytology favours neoplasia
Invasive carcinoma	Colposcopy with biopsy or conisation; treat confirmed

Aadapted from Anderson JR. A guide to the clinical care of women with HIV-2005 edition. Published by US Department of Health and Human Services, Health Resources and Service Administration, HIV/AIDS Bureau. http://hab.hrsa.gov/publications/womencare05

Table 5.3-1 Recommended management of abnormal Pap-smear

Diagnosis of HPV is through the physical examination, colpascopy and Pap smear. Colpascopy helps to determine cervical lesions. Most common cervical signs of HPV infection are flat condylomas, dysplasia, CIN, carcinoma in situ, and cervical cancer. Pap smear is method of cervical cytology screening, which sensitivity ranged from 31% to 89%. The Pap test can detect all types of epithelial abnormalities, including atypical squamous cells, low–grade aquamous intraepithelial cells, high-

grade intraepithelial cells, squamous cell carcinoma, atypical glandular cells, and cervical adenocarsinoma. (Table 5.3-2)

Cytological classification (used for screening)		Histological classification (used for diagnosis)	
Pap	Bethesda system	CIN	WHO descriptive classifications
Class I	Normal	Normal	Normal
Class II	ASC-US ASC-H	Atypia	Atypia
Class II	LSIL	CIN 1 including flat condyloma	Koilocytosis
Class III	HSIL	CIN 2	Moderate dysplasia
Class III	HSIL	CIN 3	Severe dysplasia
Class IV	HSIL	CIN 3	Carcinoma in situ
Class V	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

Table 5.3-2 Cytological and hystological classification of cervical epithelial abnormalities

The main goals of treatment for HPV are eliminating of the warts and reliefe of symptoms. There are two methods of treatment: pharmacological and surgical. Topical medicamentous therapy includes administration of podophyllin, podofilox and imiquimod. Surgical treatment include surgical excision, electrocautery, cryotherapy, and CO2 laser vaporisation .

For prevention of some types of HPV an HPV-like particle vaccines are available: Gardasil, against 4 HPV serotypes (6,8,16,18), and Cervarix, against HPV types 16 and 18. These serotypes are responsible for 70% of cervical cancer and 90% of genital warts. In some countries HPV

vaccines are included to the general vaccination program, and are used in females aged 9 to 26. These vaccines are effective in patients before the onset of sexual life.

Pelvic Inflammatory Disease

This is an inflammation of the upper reproductive organs, including the uterus, fallopian tubes, and ovaries. PID is a common cause of pain in the pelvic and abdominal areas, but can often be present for some time without causing obvious symptomes. Microorganisms from the lower genital tract ascend through the cervical canal to upper genital organs and cause inflammation of these organs. Endometritis, salpingitis ,and peritonitis developes. If left untreated, PID can lead to infertility and ectopic pregnancy.

The World Health Organisation estimated that approximately annual rate of PID has been reported as high as 10-20 per 1000 women of reproductive age. The classic high-risk patient is a menstruating woman younger than 25 years who has multiple sex partners, does not use contraception, and lives in an area with a high prevalence of STI's. The most common infections associated with PID are C.trachomatis, N.gonorrhoea, G.vaginalis, Mycoplasma genitalium. Laporascopic studies have shown that in 30-40% of cases, PID is polymicrobal.

PID develops in 20-30% of women with inadequately treated chlamydial and gonococcal infections. The mechanism of ascending of microorganisms from lower genital tract is not clearly known. Vaginal

inflammation, hormonal dysbalance, antibiotic treatment of STI's, that disrupt the normal vaginal flora, causing overgrow of normally nonpathogenic organisms, rhythmic uterine contractions during intercourse, douching are predisposing factors for infection ascending.

The symptoms of PID can vary , and include the following:

-lower abdominal pain and tenderness

-abnormal vaginal discharge

-dysuria

-irregular vaginal bleeding

-high fever and chill

-dyspareunia

-nausea and vomiting

Sometimes PID's duration is asymptomatic.

Diagnosis of PID should begin with a detailed history of the disease, physical examination, including palpation of the abdomen, speculum and bimanual examination of the vagina, blood tests, including complete blood count, leukosytosis, erythrocite sedimentation rate, C-reactive protein level, pelvic ultrasonic examination and diagnostic laparoscopy. Abnormal findings as abdominal tenderness, fever, elevated ESR and C-reactive protein level, and documented cervical infections with chlamydia or gonorrhea are making the diagnosis of PID more reliable.

Treatment should be started immediately. The goal of treatment is to eliminate infection of the genital tract and inflammation, reliefe of symptoms, prevention of long-term sequelae. Patients with severe symptoms should be hospitalised. Antibiotic therapy appropriate to the causative agent should be administered. Depending on severity of symptoms the disease can be treated by oral or intravenous antibiotics or their combination. If abscesses have formed surgical operation is needed. Reevaluation of patients should be done 3-4 weeks after treatment.

PID can result in adhesions and scarring of fallopian tubes, leading to infertility, ectopic pregnancy and chronic pelvic pain.

Prevention of PID is a decreasing of incidence of STI by regular gynecologic check-ups and screenings.

Chapter review

1. Development of adhesions in the pelvic cavity is characteristic for:

A) Gand chlamydia

B) Gardnerella vaginalis

C) Ureaplasma

D) Herpes genitalis

E) Candidiasis

2. Why inflammatory diseases of upper genital organs lead to infetility?

A) Bacause of the development of adhesions that makes the tubal cavity occlusion

B) They increase sensibilisation to eyaculate

C) Lead to development of cervix erosion

D) Lead to ovarian dysfunction

E) Lead to endocrine disorders

3. Which organ is commonly attacked by Chlamydia?

A) Fallopian tubes and cervix

B) Vagina

C) Myometrium

D) Endometrium

E) Ovaries

4. It’s not characteristic for chronic endometritis:

A) High fever ,chill,acute pain in the lower abdomen

B) Infertility and miscarriage

C) Chronic pelvic pain

D) Serous-purulent cervical discharge

E) Presence of intrauterine adhesions

5. Which of the following is not characteristic for bacterial vaginosis?

A) Disuria

B) Presence of the clue cells

C) Ph of the vagina >4.5

D) Presence of creamy white-grayish discharge

E) Positive amine test

6. Most common microbial association for bacterial vaginosis is:

A) Gardnerella, bacteroides, mobilincus

B) Trichomonas, stafilococcus

C) N.gonorrhoea, candida albicans

D) Clebsiella,n.gonorrhoea

E) Candida albicans, shigella

7. Trichomonada vaginalis is:

A) Protozoa

B) Bacteria

C) Virus

D) Parazite

E) Yeast

8. It’s not characteristic for viral infections of genitalia:

A) Lesions of fallopian tubes

B) Sexually transmitted infection

C) Highly contagious

D) Recurrent duration

E) High oncogenic potencity of the pathogen

9. Which infection is an etiologic agent for cervical cancer?

A) HPV

B) Genital herpes

C) Chlamydia

D) Genital tuberculosis

E) HIV

10. The most informative method of diagnosis of cervical dysplasia is:

A) Hystologic examination of cervical tissue

B) Colposcopy

C) Curretage of the cervical canal

D) Rectovaginal examination

E) Endometrial biopsy

Chapter 6 Infertility

6.1 Definition,Etiology,Diagnosis and Treatment

Infertility is a failure of a couple to conceive after a year of having regular intercourse without contraception. It is estimated that 15-18% of couples are infertile. Infertility is very actual medical and social problem. As a result of a numerous studies within the framework of the international programmes of the WHO, standartized algorithm for diagnosis and treatment of a female infertility has been developed and applied to the clinical practice. Introduction of the endoscopic methods of examination into the clinical practice allowed to objectively analyze the structure of female infertility ,and determine that the leading causes of the generative function violation are : tubal occlusion (37-38%), external genital endometriosis (27-30%), problems with ovulation (18-30%), and others (8-12%). Most common infertility factors in infertile couple are presented in a Figure 6.1-1

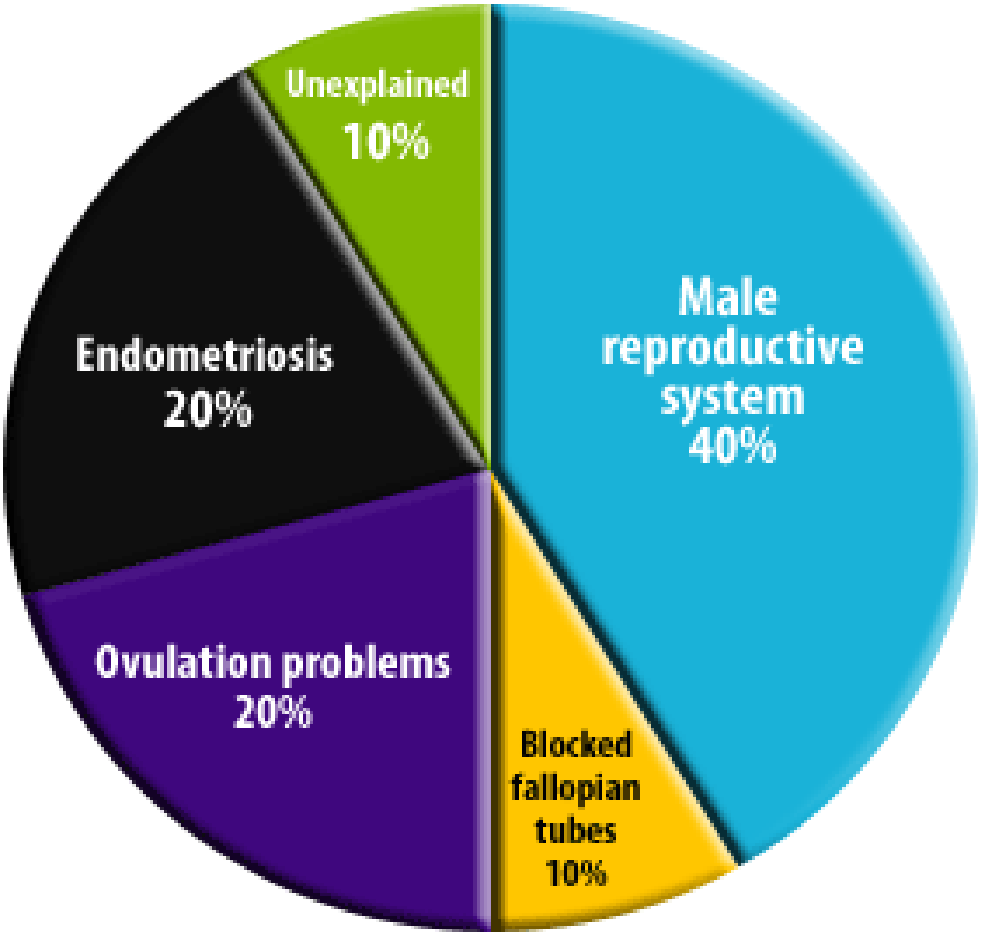


Figure 6.1-1 the most common factors of infertility

Infertility is classified to primary and secondary. Primary infertility is considered when it occurs without any prior pregnancies; secondary when it follows previous conception. Even when fertilization occurs, it is estimated that approximately about 70% of embryos are abnormal and this pregnancies result in spontaneous or missed abortions. Studies show that more than 80% of couples conceive within first year of a sexual life. Average age of infertile women is approximately 33.1+- 1.7 year in average duration of infertility 6.9+-1.4 year. Age of women 35 and more decreases the rate of conception because of lower embryo quality,

reduced ovulation, and possible decreased frequency of sexual intercourse.

Investigations of the infertile couples proved that the efficiency of reproductive function restoring depends on tree major factors:

-evaluation of the reproductive function by standardized algorithm of examination

-diagnosis of the infertility causes

-conduction of integrated phased therapy due to clinical type of the disease

Initial evaluation of the patients involves noninvasive and relatively simple tests. Gynecologic history includes detailed information about present illness, menstrual, sexual functions, family and hereditary anamnesis, duration and result of previous pregnancies. Physical examination includes determination of the body type, body mass index, breast development, hirsute number by Ferriman-Gallwey score, and presence of galactorrhea. Gynecological examination for determination of anatomical and congenital abnormalities and colposcopy for evaluation of the cervix are neccessary.

Infertility in about 40% of infertile couples has multiple causes. In 5-10% of couples idiopathic infertility can be found.

Male factor

It’s one of the key problems of andrology. The incidence of male infertility is increasing, and it is average 30-50 %. Main causes of male infertility are: genital tract infections, such as prostatitis, mumps orchitis, primary failure of testis function as a result of some chronic and chromosomal diseases, trauma or surgery of male genitalia, occlusion of the VAS ductus, exposure of the some medications, radiation and chemotherapy, alcohol abuse, excessive smoking and psychological factors.

Diagnosis of male infertility includes: history, physical examination, urogenital examination, laboratory tests, and US examination.

A semen analysis should be performed following a 2 to 4-day period of abstinence. If semen is abnormal, at least three consecutive analyses should be done for accurate evaluation. Characteristics of the semen are presented in the Table 6.1-1

Volume	≥ 2.0 ml
pH	7.0-8.0
Sperm concentration	≥ 20 million / mL
Total no. of spermatozoa	≥ 40 million / ejaculate
Motility	≥ 50% with progressive motility or 25% with rapid motility within 60 min after ejaculation
Morphology	≥ 14% of normal shape and form*
Leukocytes	< 1 million / mL
Immunobead test	< 50% spermatozoa with adherent particles
MAR-test**	< 50% spermatozoa with adherent particles

*Assessment according to Kruger and Menkfeld criteria, **MAR - Mixed antiglobulin reaction

Table 6.1-1 Characteristics of a normal semen

Hormonal screening gives information about presence of some disease. So, low levels of gonadotropins and testosterone may indicate hypothalamic-pituitary failure; elevated FSH level indicates substantial parenchymal damage of the testes; elevated level of prolactin is indicator of prolactin-producing tumor of the pituitary gland.

As infections of the genital tract are one of the factors of male infertility, analysis on determination of chlamydia, ureaplasma, mycoplasma, genital herpes and cytomegalovirus are indicated.

Treatment of male infertility depends on a cause of infertility and divides on conservative and surgical. Conservative methods of treatment are beneficial at infectious, endocrine and psychological violations. Antibiotics, hormones and immunostimulators are administered appropriate to the existing problem. Hormonal therapy includes administration of androgens, antiestrogens, gonadotropins, releasing-hormones, prolactin inhibitors.

Surgical treatment is indicated if varicocele exists. Ligation of the venous plexus improves semen quality.

Sperm washing and intrauterine insemination is one of the effective methods for achieving of conception. Indications for IUI are:

-subfertile indicators of semen

-anatomical-functional failure of reproductive system

-immune factor

-abnormalities of semen volume

-retrograde ejaculation

IVF and ICSI (intracytoplasmic sperm injection) are effective treatment of male infertility as well.

Prevention of the male infertility encompasses early determination of the developmental abnormalities of the reproductive system, diagnosis, treatment and prevention of the diseases influencing fertility.

Tubal –peritoneal factor

Tubal –peritoneal factor of infertility occupies first place in the structure of etiologic causes, and its incidence is about 40-60% of all female infertility cases. Main causes of tubal-peritoneal infertility are: infections of the genital tract, most commonly gonorrhea, chlamydia, ureaplasma, mycoplasma, tuberculosis, genital herpes ; formation of the adhesions as a result of medical interventions and complications of surgical operations; and endometriosis . The incidence of a tubal damage after one episode of pelvic infection is about 12%, 23% after two episodes, and 54% after three episodes. Tubal occlusion may occur at three locations: isthmic part, the mid-segment, and the fimbrial end. Fimbrial occlusion is the most common. Another special group with tubal infertility consists of those patients who desire reversal of their tubal sterilization.

The diagnosis of tubal-peritoneal infertility based on radiologic and laparoscopic findings. The main method for diagnosis of tubal abnormalities is hysterosalpingography (HSG). It is a radiologic procedure, based on injection of a radio-opaque dye into the uterine cavity with following series of images under fluoroscopy. This method allows evaluation of the shape and structure of the uterus, the fallopian tubes and determination the presence and severity of abnormalities of these structures. The best time for performing HSG is one week after menstruation, but before ovulation. In case of active inflammatory process HGS is contraindicated. Anesthesia is not required. A water-soluble or oil-soluble dye is used. In some cases HSG has therapeutic effect. (Figure 6.1-2)

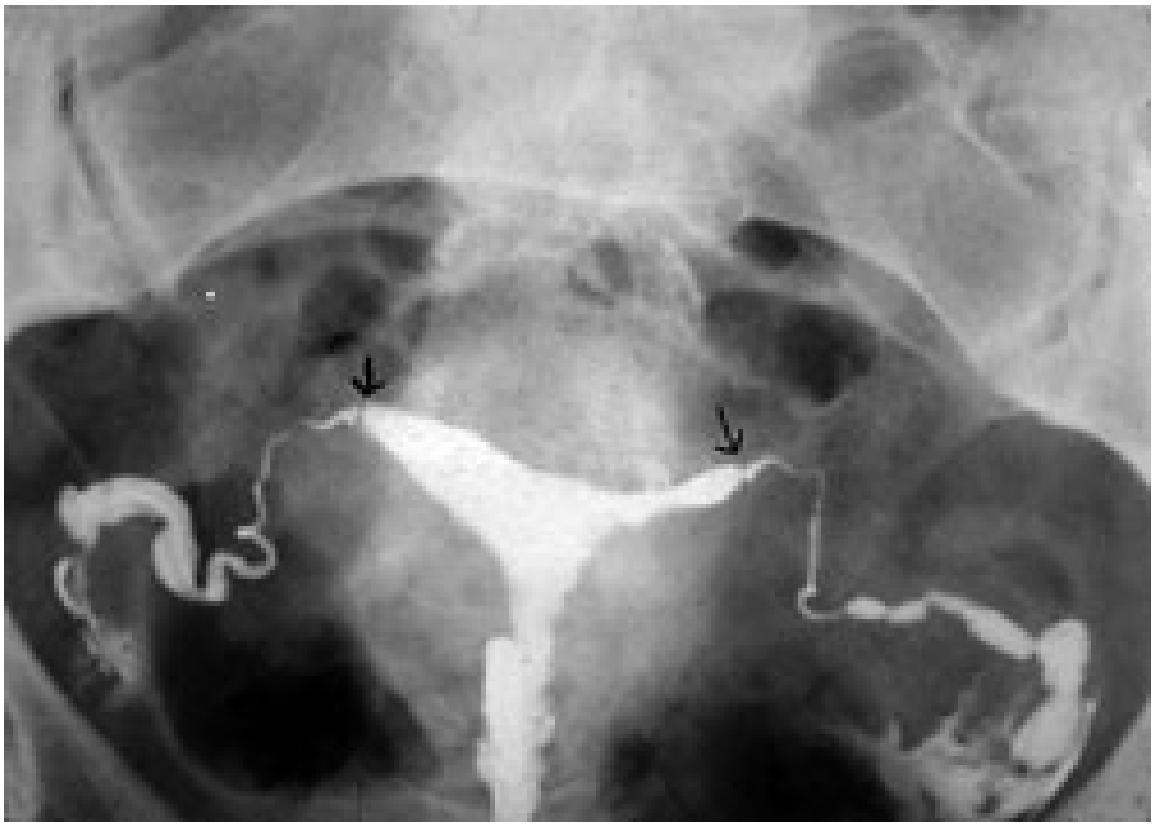


Figure 6.1-2 X-ray imaging of the uterus and fallopian tubes during HSG

Laparoscopy help to identify pathologic conditions associated with infertility in 30-50% of cases of unexplained infertility. Usually, the most common finding is endometriosis. Information about the incidence of infertility due to endometriosis is contradictory but convincing. Endometriosis may lead both to tubal occlusion and hormonal violations. (Figure 6.1.-3)

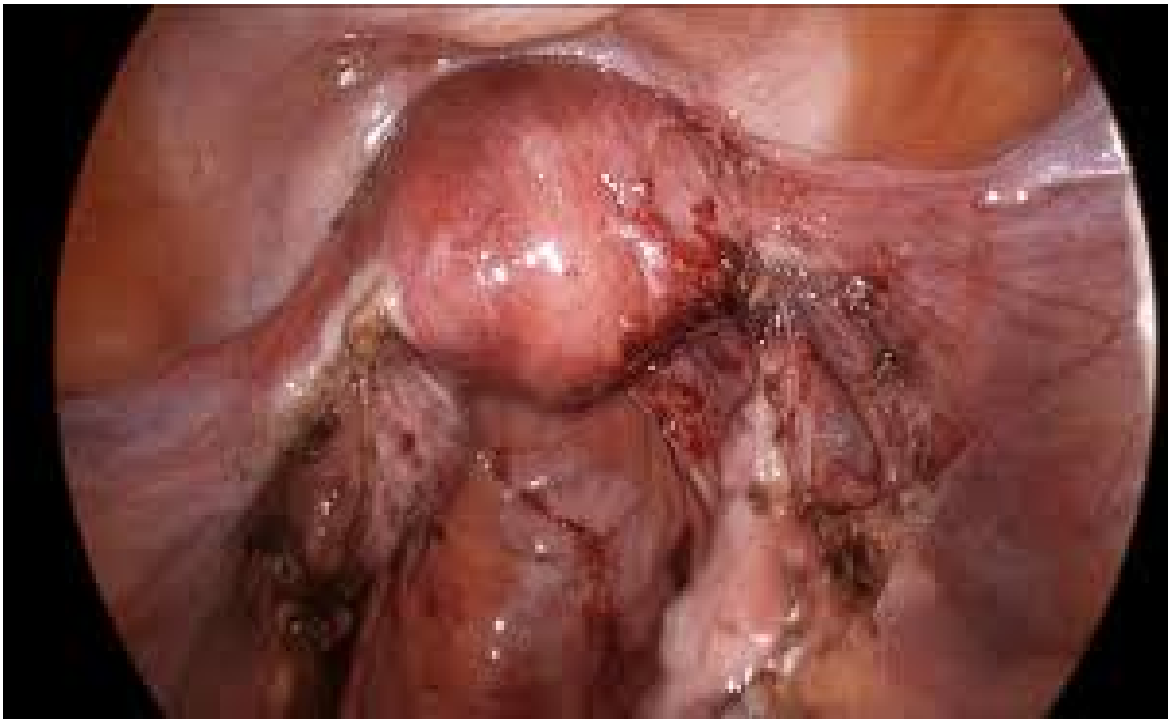


Figure 6.1-3 Laparoscopic imaging of the pelvic endometriosis

Treatment of tubal occlusion is directed on restoration of patency of the fallopian tubes. In most circumstances, microsurgical tuboplasty is more

effective than conventional surgical techniques for reversal of tubal occlusion. In case of fimbrial occlusion the success rate of neosalpingostomy is 20-30%. If the intramural portion of the tube is occluded, reimplantation with a new opening into the endometrial cavity is required. Operations are usually done by laparoscopy. Most common complication of these operations is ectopic pregnancy.

In case if external genital endometriosis is suspected laparascopy is a choice for diagnosis and first step treatment. With advanced operative laparoscopic techniques destruction or ablation of the endometriosis foci, lysis of adhesions and endometriomas removal should be performed. Second step of treatment is administration of GnRH agonists, which decreases the level of endogenous ovarian hormones, and consequently reliefs the symptoms of endometriosis.

In absence of pregnancy within 12 month after treatment IVF is indicated.

Ovulatory factor

Synthesis and introduction to clinical practice stimulators of ovulation allowed achieving significant progress in the treatment of women with ovulatory infertility. Some women do not ovulate regularly due to hormonal changes, and it reflects on their ability to conceive. There are two types of ovulatory disorder : anovulation, in which eggs do not develop properly , or are not released from the follicles of the ovaries; and oligo-ovulation , in which ovulation doesn’t occur on a regular basis

and usually is found in women with length of the menstrual cycle 35 days and more.

Anovulation or oligo-ovulation can be caused by a number of factors. The most common causes are: PCOS, obesity, low body weight, hyperprolactinemia, premature ovarian failure, advanced maternal age, thyroid dysfunction, stress.

The simplest screening test to confirm ovulation are serial measurement of urinary LH, which assesses the duration of luteal function, and the mid-luteal level of serum progesterone . The following laboratory tests are helpful in diagnosis of ovulatory dysfunction: blood levels of FSH, progesterone, ultrasound, endometrial biopsy.

The most common treatment for anovulation is fertility drugs. Clomiphene citrate or gonadotropins are used to correct any luteal insufficiency. Clomiphene citrate can trigger ovulation in 80% of anovulatory women, and help about 45% get pregnant within six month s of treatment.

The choice of the most appropriate technique for ovulation induction is specific and depends on a cause of ovulatory dysfunction. So, in case of pituitary insufficiency combination of exogenous gonadotropins with injection of HHG is most effective. Subcutaneous or intravenous administration of GnRH in a small pulsatile rejimen every 90-120 minutes by an infusion pump for treatment of hypothalamic amenorrhea is very effective, and helps to achieve pregnancy in 70-75% of cases. Patients with hyperprolactinemia are successfully treated by

bromcriptine without administration of ovulation inductors; efficiency of treatment is 74.2%.

The only method of achieving of pregnancy in patients with premature ovarian failure is IVF with donor egg.

In patients with PCOS induction of ovulation is more effective in combination of clomiphene citrate with gonadotropins and metformin. Assessment of ovulation is done by serial pelvic ultrasound. If ovulation does not occur by stimulation, but follicular development is occurring, then administration of hCG is administered. If follicular maturation is not occurring, ovulation induction will require low dose FSH or hMG. Administrating of FSH for induction of ovulation in patients with PCOS is very promising and its efficiency is approximately 50%.

The main complications of ovulation induction are the hyperstimulation syndrome, associated with significant ovarian enlargement and ascites, and multifetal pregnancy.

6.2 Assisted Reproductive Technologies

In the absence of the positive results from the traditional methods of treatment of infertility, the last resort for infertile couples is IVF and embryo transfer. It is the most effective modern method of treatment of almost all types of infertility. IVF (in vitro fertilization) is a method of fertilization outside the human body in a laboratory glass with further transfer of embryo into the uterine cavity. (Figure 6.2-1)

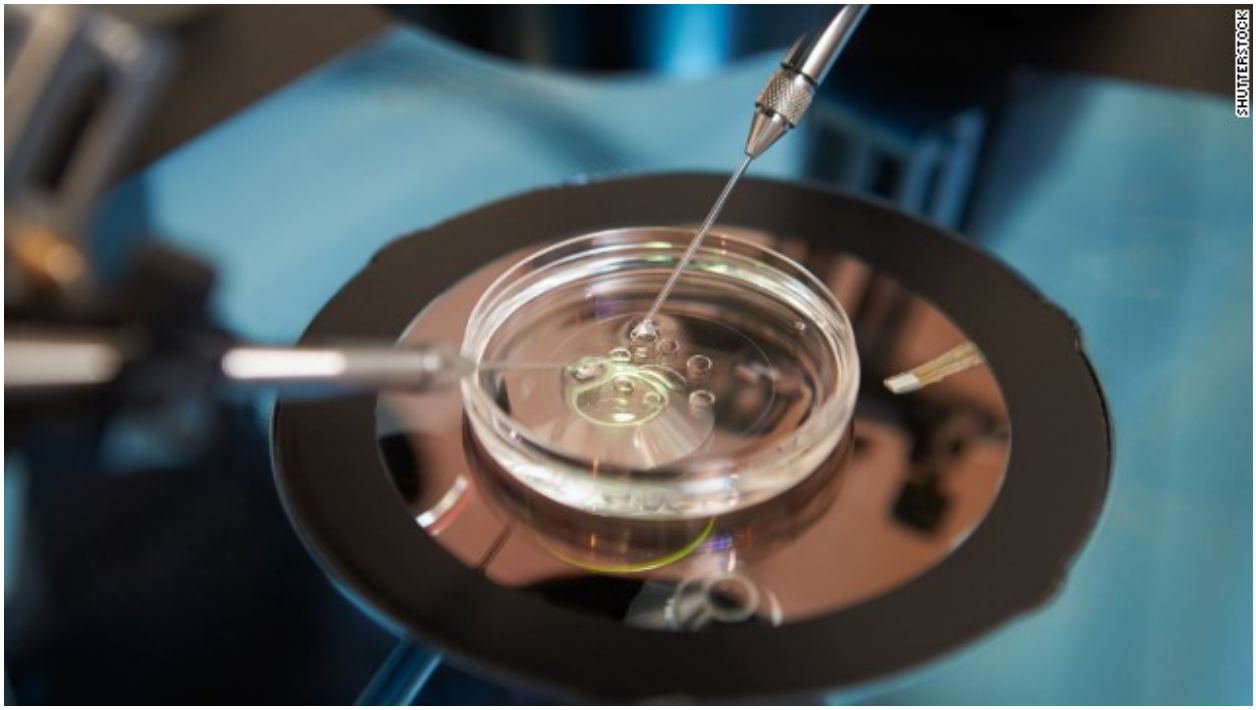


Figure 6.2-1 Process of IVF in a laboratory glass

At the present time there are some new lines of IVF, which are very effective and promising:

-donation of oocytes

-intracytoplasmic injection of the sperm

-carrying of pregnancy by surrogate mother

-preimplantation diagnosis of the fetus

The first successful IVF procedure was made in 1978 in England. Now, more than 1 million children all over the world were fertilized by IVF. And this number is increasing. It is a treatment of choice in such factors of infertility, as total tube occlusion and male factor. Fertilization rates are high, approximately 30-35%.

For IVF and embryo transfer first procedure that woman should be done is induction of ovulation. A GnRH agonist is given to prevent premature LH release. Treatment is usually startet in the mid-luteal phase. Then ovaries are stimulated with FSH, hMG, or both, on the second or third day of the next menstrual cycle. Dosage and duration of stimulation determined by US scan and hormonal monitoring of the ovaries. As follicle reaches 18-20 mm in diameter with thickness of endometrium 8-10 mm and blood level of estradiol 300 pmol/l, intramuscular injection of ovulatory dose of hCG is given. 35 hours after hCG injection, multiple oocytes are aspirated under transvaginal US control. After that oocytes are fertilized by washed sperm or a single sperm injection in vitro. Fertilization may be evaluated by the vizualisation of two pronuclei 19 to 20 hours after the procedure. A day 2 to 5, in a stage of 2-8 blastomers, embryo is transferred into the uterine cavity by a tiny catheter. It is not allowed to transfer more than 2 or 3 embryos. At the present most IVF centers propose the transfer of a single embryo for better outcomes.

Preimplantation diagnosis of embryo gives possibility for prevention of chromosomal abnormalities, especially in those families with hereditary diseases. For determination of chromosomal abnormalities FISH and PCR analysis are used. Biopsy of embryo is conducted at day 2-3 in a stage of 4-12 blastomers.

For women with premature ovarian failure IVF with donor oocyte is the only method to achieve pregnancy. The egg from young fertile women is used. It gives possibility to have a child even for women without the ovaries.

Chapter Review

1. Hormomal infertility is not a result of the following disease:

A) Dysgerminoma

B) Adrenogenital syndrome

C) Prolactinproducing tumor of pituitary gland

D) PCOS

E) Hypothalamo-pituitary dysfunction

2. Aspermia is:

A) Absence of ejaculate

B) Concentration of sperm < 20x10’6/ml

C) Absence of sperm in the ejaculate

D) Morphologically normal sperm < 14%

E) Decreasing of a sperm mobility

3. Primary infertility is:

A) Absence of pregnancy at all

B) Absence of stillbirth child

C) All pregnancies were interrupted by medical indications

D) Agenesia of upper reproductive tract

E) Menstrual dysfunction

4. Occlusion of the fallopian tubes occurs as a result of:

A) Inflammatory diseases of reproductive organs and endometriosis

B) PCOS

C) Hypofunction of pituitary gland

D) Hyperandrogenia

E) Stress

5. This method is used for diagnosis of interstitial tubal occlusion:

A) Hysterosalpingogrphy

B) Colposcopy

C) Laparotomy

D) Endometrial biopsy

E) Laparoscopy

6. The treatment of choice for patients with premature ovarian failure is:

A) IVF with donor oocyte

B) Stimulation of ovulation

C) Intrauterine insemination

D) Administration of GnRH

E) Laporascopic drilling of the ovaries

7. It’s not indication for IVF;

A) Hyperprolactinemia

B) Premature ovarian failure

C) PCOS

D) Total tubal occlusion

E) Aspermia

8. It is favorable time for embryo transfer:

A) 3-5 days of fertilization

B) 1-2 days of fertilization

C) Immediately after fertilization

D) 2 weeks of fertilization

E) 1-2 days after ovulation

9. The most common pituitary disorder which doesn’t cause anovulation is:

A) Acromegaly

B) Prolactinoma

C) Empty sella turcika

D) Sheehan syndrome

E) Cushing syndrome

10. What are the causes of male factor infertility?

1. Varicocele

2. Testicular failure

3. Tubal occlusion

4. Endometriosis

5. Infections

A) 1, 2, 5

B) 2, 3, 5

C) 1, 2, 4

D) 3, 4, 5

E) 1, 3, 5

Chapter 7 Benign Disorders of the Upper Genital Tract

7.1 Uterine Myoma

Uterine myomas are benign hormonal depending tumors derived from the smooth muscle cells of the myometrium and develop in women of reproductive age. They are most common tumors of the uterus. They may be single or multiple. Uterine myomas diagnosed in 4-12% of women in general population, 20% of cases in forth and 40% of cases in fifth decade of their life. Despite myomas are benign tumors, they followed by a range of endocrine-metabolic changes with high incidence in perimenopausal period. Malignant potensial of myomas is very low, but the studies show, that incidence of endometrial cancer increases in women with uterine myomas , especially in those with asymptomatic duration of the disease.

Factors that initiate uterine myomas are not known, but it suggested that viloations in excretion and metabolic aromatization of estrogens, and disproportions between estrogen fractions lead to morphological changes in the myometrium. Myomas mass may increase equally often as a result of smooth muscle cells hyperplasia induced by estrogens, so their hypertrophy as well. Myomas rarely develop before menarche and after menopause. They are rich with estrogen and progesterone receptors, which are highly sensitive to hormonal stimulation. If estrogens stimulate proliferation of smooth muscle cells and enlargement of the myomas, so progesterone increases the production of the proteins that interfere with apoptosis (programmed cell death). Myomas also consist of fibrotic connective tissue elements, generally fibronectin and collagen that form extracellular matrix of these tumors.

Along with the hormonal aspects of the pathogenesis of the myomas, additional influence on their development have such factors as changes

in organism immunity, age, changes in the hemodynamics of the pelvic cavity, ethnicity, and family history.

By morphogenetic signs there are three types of myomas:

-simple myomas

-proliferating myomas with high score of enlargement

-presarcomatic myomas

By location uterine myomas classify on:

-submucosal that grow towards the endometrium. Sometimes they can extend through the endometrial cavity and abort from the cervical canal

-subserosal that grow toward the abdominal cavity

-intramural, arise within the myometrium

-intraligementar, arise between the sheets of the broad ligament

-cevical, arise within the cervix

-parasitic, that lose the connection with the uterus and attached to the blood supply (Figure 7.1-1)

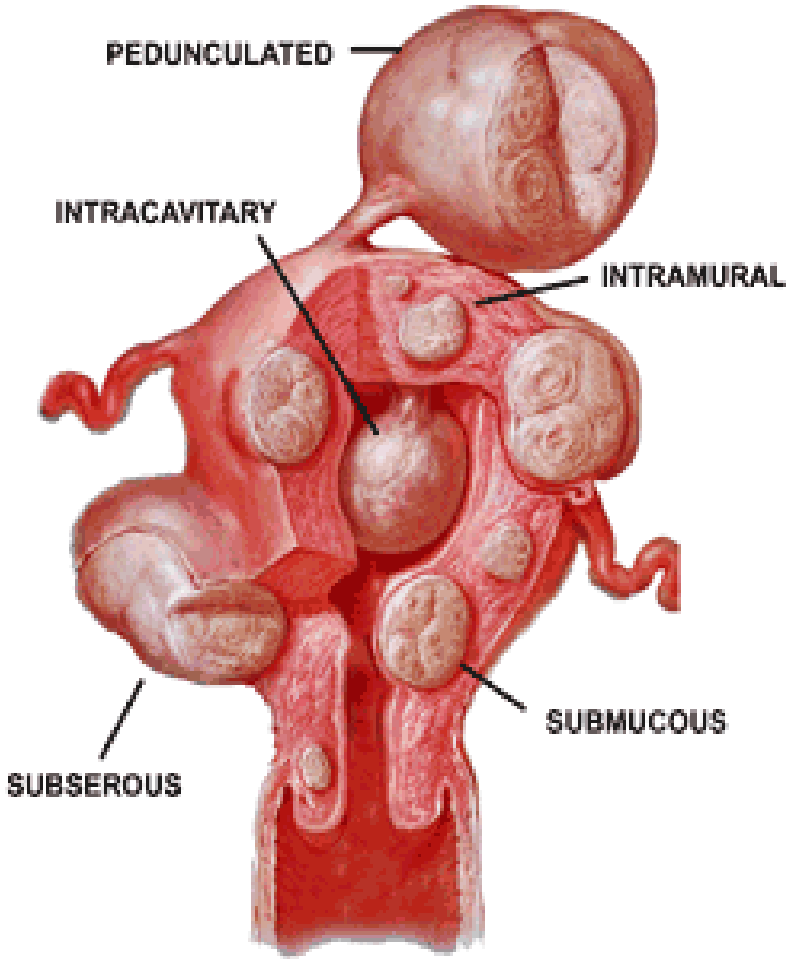


Figure 7.1-1 Uterine myomas in various anatomic locations

Uterine myomas are generally spherical, white, firm lesions. They have no true capsula. Pseucapsula consist of fibrotic and muscle elements that compressed to the periphery by enlarged tumor mass. Blood circulation is more evident on the periphery, so the central part of the myomas very often exposed to degenerative changes. Most common degenerative change is hyaline acellularity. Also infection, malignisation and calcification may occur. Cystic transformation of the myomas usually occur as a result of red degeneration – aseptic necrosis and local hemolysis that myoma may undergo during pregnancy.

Incidence of transformation of the myoma to sarcoma is less than 1% of cases.

Clinical manifestation of the myoma depends on their location and size. Single subserosal and intramural myomas may have no clinical symptoms at all for a long period of time, until they significantly increase in size and undergo to destructive changes.

Some myomas, especially subserosal, may enlarge to 10-25 cm in diameter. In these cases they contribute to pain associated with increased pelvic pressure, compression of the nerve plexus, stretching of the visceral peritoneum. Patients may complain on heaviness in the lower abdomen, bloating, lower back pain, dysuria, congestion as a result of compression of the neighbor organs. (Figure 7.1-2)

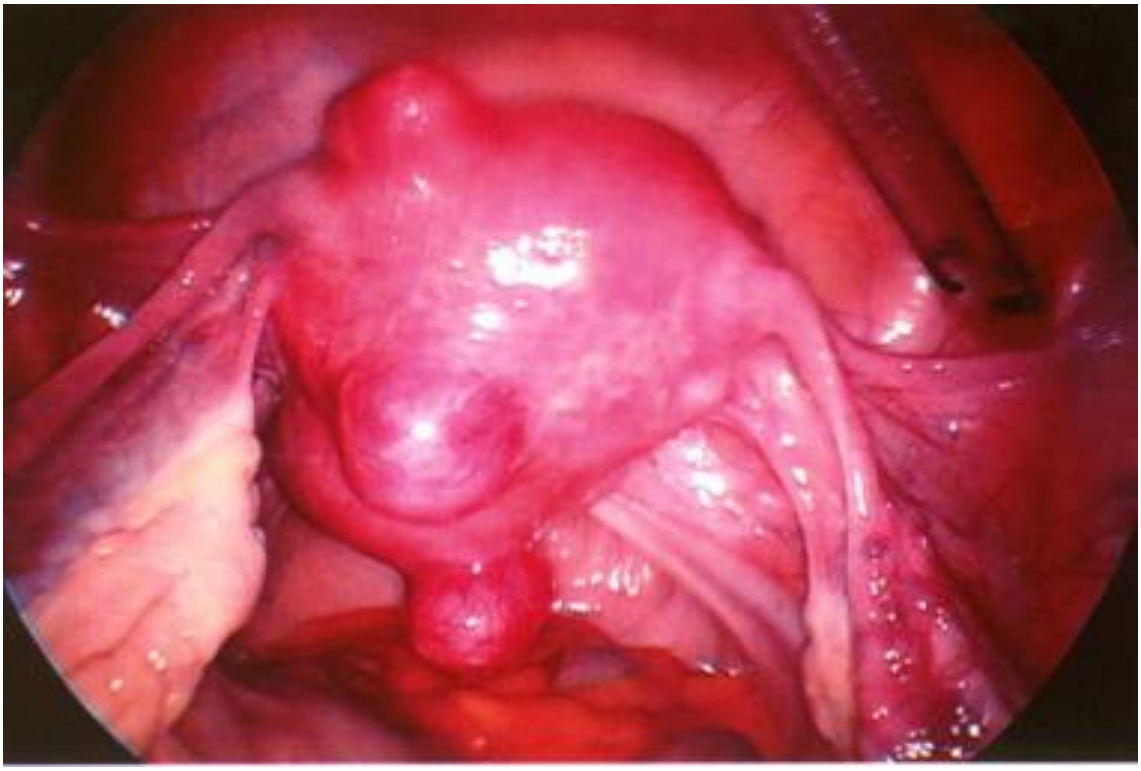


Figure 7.1-2 Laparoscopic view of uterine myomas

Intramural and submucosal myomas may lead to violation of uterine contractility. Patients complain on prolonged heavy menstruations and metrorrhagia. Excessive bleeding may result in anemia, weakness, congestive heart failure.

Symptoms of acute abdomen develop in case of red degeneration within a tumor, and necrosis of the myomas as a result of the twisted pedicle.

Combination of the intramural, subserosal and submucosal myomas associated with more diverse clinical signs.

Large myomas, located the close to tubal cornu, may occlude the interstitial part of the fallopian tubes and increase incidence of infertility.

Bimanual examination and US imaging are used for diagnosis of uterine myomas. Large myomas can be palpated abdominally. On bimanual examination myomas are felt like spheric, firm nontender formations, separately from the uterus if they are subserosal. The uterus is enlarged and has abnormal shape, its surface become bumpy. The consistence of the tumors varies from hard rock to soft or cystic in case of cystic degeneration. Intraligamentory subserosal myomas are defined by the sides of the uterus, and sometimes indistinguishable from the adnexal mass. For submucosal myomas it is characteristic symmetrically enlarged uterus. Submucosal myomas may arise through the endometrial cavity to the cervical canal and abort from it can be observed during vaginal examination with speculum.

Before bimanual examination the bladder should be emptied.

US imaging is widely used for diagnosis of topographic location, size of the myomas and help to identify them from the adnexal mass. (Figure 7.1-3)

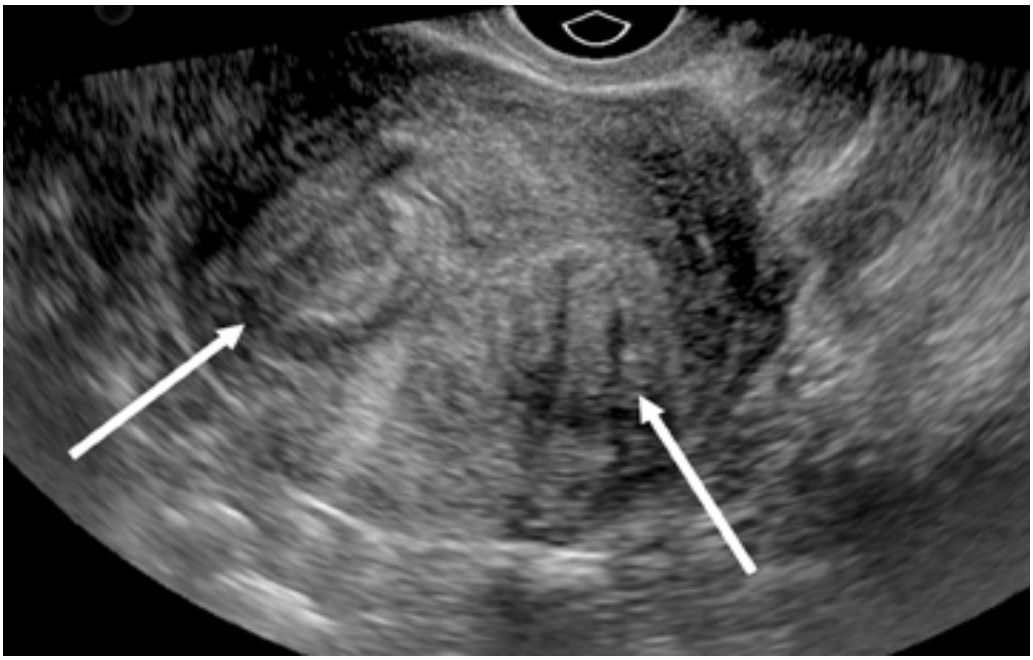


Figure 7.1-3 Ultrasound image of a uterus enlarged by multiple myomas

For differential diagnosis of the uterine myomas from other uterine pathologies along with the US imaging, CT and MRI are used. The most common differential diagnosis are normal pregnancy, an ovarian tumors, tumors of the colon, pelvic kidney, adnexal abscesses, diverticular or inflammatory bowel mass , retroperitoneal tumors. In some cases diagnostic laparoscopy is indicated.

There are three main treatment options for the uterine myomas:

-medical management

-surgical treatment

-minimally invasive organ-preserving treatment

Medical management is used with the purpose of inhibiting the growth or reverse tumor development, and treatment of heavy and prolonged menstruation. Combined oral contraceptives and progestine-only therapies, including levonogestrel-releasing intrauterine devices, are the first step of treatment. The main purpose of this therapy is to decreas bloodloss during menstruation, discontinue monthly proliferation of the endometrium, and thus, lead to reducing of the menses.

GnRH agonists influence the myomas growth. Administration of these drugs is advisable to patient in perimenopausal period and patient before the surgical treatment, because they induce reduction of steroidogenesis and menopause. Climacteric symptoms as hot flashes, decreasing of bone density, depression are developed. That’s why only short course of these agonists can be administered. They are also economically inefficient due to the high cost.

Gonadoliberin antagonists are directly competitive blocking GhRH receptors in the pituitary gland, and thus, lead to decresing of LH and FSH production. Compared with GnRH agonists, administration of gonadoliberin antagonists are more favorable for treatment of the patients with uterine myomas.

Antigestagens or antogonists of the progesterone act on progesterone receptors. Administration of these drugs has shown good clinical effects as reduction of the size of the myomas.

Despite the success achieving in medical treatment of the myomas, surgical treatment remains the leading. Incidence of surgical treatment of uterine myomas is 45% among all surgical interventions in gynecology. Type and volume of the surgical treatment depends on many factors. So small intramural, subserosal and pedunculated myomas may be removed laparascopically. Laparatomy is indicated for treatment of very large myomas. Hysterectomy or myomectomy is performed. Hysterectomy can be done by laparotomy, laparoscopy or intravaginally. The volume of the surgical treatment depends on desire of patients to preserve their fertility as well.

Minimally invasive procedures have been developed as alternative treatment options for uterine myomas. Cryomyolysis and uterine artery embilozation are treatment of choice. MRI –guided procedure of uterine artery embolization by catheterization of the femoral artery and transfer of the embol to the uterine artery decreases blood supply of the tumor. As a result myomas are reduced in size and their further growth is interrupted. Cryomyolysis is a technique for destroying the myoma by cooling, using liquid nitrogen that results in reducing the volume of the myomas due to protein denaturation and necrosis.

Regular gynecological examinations give possibility to early diagnosis of the myomas, and reduce incidence of surgical interventions.

7.2 Endometrial Hyperplasia

Endometrial hyperplasia is one of the basic forms of proliferative changes of the uterine mucosa in women of different age groups. Endometrium is a target tissue sensitive to hormonal changes occurring in the body. Estrogens are the main contributors to endometrial proliferation.

Failure in neuro-endocrine regulation of reproductive function reflects on relationship between gonadotrops and sex hormons. Persistency of the follicle or it's atresia, followed by anovulation, promotes insufficiency of the lutein phase. Decreasing progesterone level leads to increasing of unopposed estrogen level, and stimulates endometrial proliferation. This process mainly occurs in women of reproductive age when ovulation is infrequent. Continuously simulation by estrogens results in excessive proliferation of the endometrium following by thickening, elongation of the gland with cystic transformation. In addition to anovulation, the following are the risk factors for developing of endometrial hyperplasia and its recurrence: PCOS, obesity, estrogen-producing tumors of the ovaries, diabetes mellitus, prolonged use of exogenous estrogens and use of tamoxifen.

In accordance with the recommendations of the WHO, hyperplastic processes of endometrium classify to:

1. Simple hyperplasia without atypia
2. Complex hyperplasia without atypia
3. Simple atypical hyperplasia
4. Complex atypical hyperplasia

Hyperplasias without atypia are considered benign pathologies which will regress with conservative treatment. Complex atypical hyperplasia has the greatest malignant potential; in the absence of the treatment up to 60% of cases progress to endometrial carcinoma within a few years. (Figure 7.2-1)

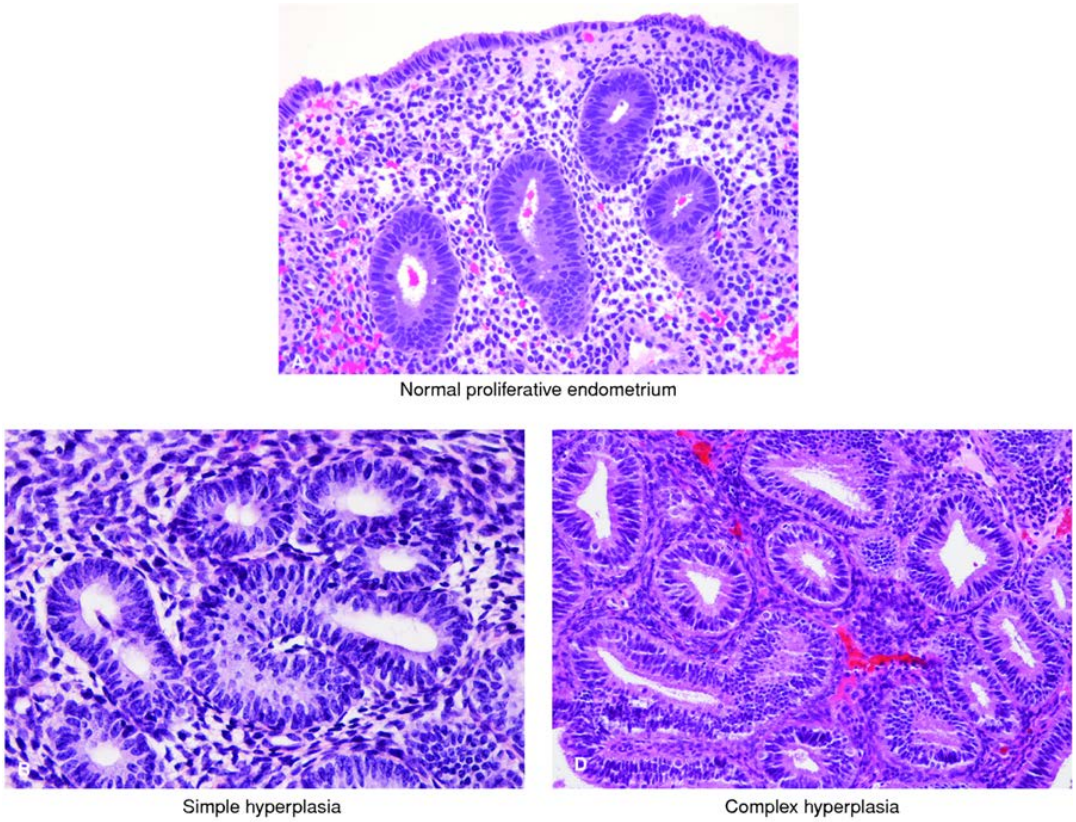


Figure 7.2-1 Endometrial biopsies of normal proliferative endometrium (A), simple endometrial hyperplasia (B), and complex endometrial hyperplasia (C)

According to the latest classification of the WHO (2014), there are 2 categories of endometrial hyperplasia:

-hyperplasia without atypia

-atypical hyperplasia/endometrioid intraepithelial neoplasia

Hyperplasia without atypia characterizes with thickening of endometrium to 1-2 cm without identification of the basal and functional layers. On the cut there are small cysts lined by simple epithelium and clear line of distinction between endometrium and myometrium.

Atypical hyperplasia characterizes with atypical cell elements, hyperchromatic nuclei, and signs of mitosis of epithelial cells, which mostly are low differenciated. Atypical hyperplasia can be found not only in hyperplastic, but in atrophic endometrium and endometrial polyps as well.

Endometrial polyps form from the epithelium of endometrium basalis and grow towards endometrial cavity. Sizes and shapes of the polyps may vary. They can be single or multiple. Surface of the polyps usually smooth with pink coloration. (Figure 7.2-2) Clinical signs of the polys are menorrhagia and spontaneous acyclic bleeding. On US imaging they have appearance of a focal thickening of the endometrial stripe. The most accurate method of diagnosis is hysteroscopy. Curettage of the endometrial cavity is not sufficiently informative, because of its flexibility and possibility to fold out from the curette.

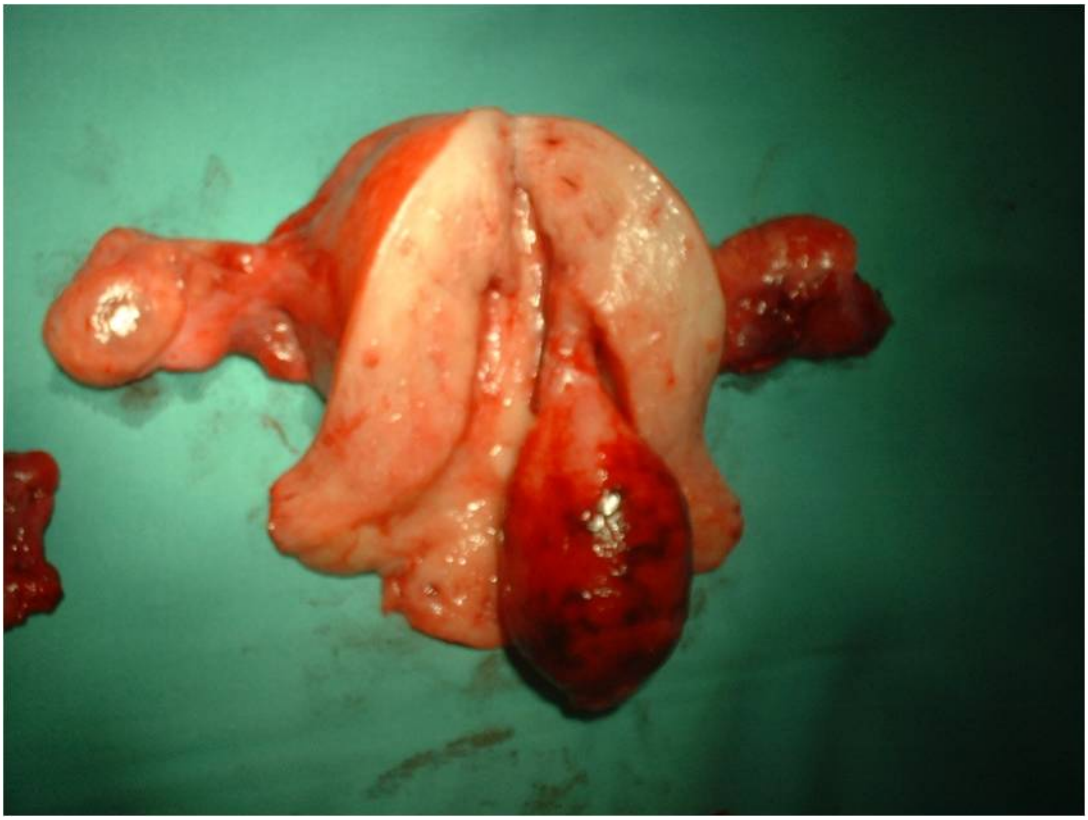


Figure 7.2-2 Giant endometrial polyp

Main clinical manifestation of the endometrial hyperplasia is excessive cyclic or acyclic uterine bleedings. Regular bleeding promote to anemia. In postmenopausal women hyperplastic processes may be asymptomatic.

Diagnosis of the endometrial hyperplasia is based on clinical findings and other methods of examination, as endometrial sampling or aspirational biopsy, US imaging, hysteroscopy.

It is expedient to perform ultrasound examination on 5-7 days of menstrual cycle. In postmenopausal women, a thin (<4 mm) endometrial stripe on transvaginal ultrasound is reassuring. Endometrial sampling usually is done 3-4 days before the estimated

menstruation, in case of uterine bleedings at first days of bleeding onset.

First –line treatment for endometrial hyperplasia without atypia is progesterone administration. Both continuous oral and levonogestrel containing intrauterine device are effective in achieving regression of endometrial hyperplasia without atypia. Duration of the treatment should be at least 6 months for achieving regression. In those patients without desire to fertilization treatment can last up to 5 years, with 6-month interval ultrasound endometrial surveillance.

Indications for hysterectomy in patients with endometrial hyperplasia without atypia are:

-absence of therapeutic effect of medical treatment and histological regression of hyperplasia after 12-month treatment

-progression to atypical hyperplasia

-combination of endometrial hyperplasia with other uterine pathologies in patients not wanting to preserve their fertility

-persistence of bleeding symptoms

Endometrial ablation is not recommended for the treatment of endometrial hyperplasia because of high incidence of endometrial adhesions and insufficient endometrial destruction.

Treatment for endometrial hyperplasia with atypia is surgical. Total hysterectomy is indicated because of the high risk of malignancy. A

laparoscopic approach is more preferable as it associated with shorter hospital stay, and quicker recovery.

7.3 Functional and Benign Ovarian Tumors

Incidence of ovarian tumors has a tendancy to increase. According to data of last ten years, it increased from 6-11% to 19-25% in a structure of tumors of reproductive organs. About 70-87% of all ovarian tumors are benign. Ovarian tumors may occur in women of all age groups. A wide variety of tumors develop from the ovaries. This is due to the fact, which ovaries consist of various elements of different hystogenesis.

Main risk factors contributing to ovarian tumors are:

-early or delayed menarche

-delayed menopause

-menstrual dysfunction

-infertility, spontaneous abortions

-chronic inflammatory diseases of adnexa

Reduction in the number of pregnancy and childbirth, resulting in continuous ovulation, and use of ovulation stimulators for the treatment of infertility, estrogens for the treatment of climacteric syndrome are also risk factors for developing of ovarian tumors.

Ovarian masses may be functional, inflammatory, metaplastic, and neoplastic.

Incidence of functional masses is approximately 34%. They develop from the follicles, by collecting of a liquid inside the follicular cavity.

Follicular cyst develops when the follicle fails to rupture. It is smooth, elastic, filled by transparent liquid cyst, lined by one or more layers of granulesa cells. In case of hemorrhage into the cystic cavity or torsion the contents of the cyst may be hemorrhagic. Some follicular cysts are hormonal active due to they are rich with estrogens. Diameter of follicular cyst may vary. It is estimated follicular cyst, if the diameter of the follicle of at least 3 cm. Sometimes it may reach in diameter 10 cm and even more.

At bimanual examination follicular cysts are usually unilocular, have smooth surface, elastic consistence and they are mobile. Generally they are asymptomatic and can be determined during the routine gynecological or US examination. Usually follicular cyst regress during subsequent menstrual cycles, so just observation during 3 menstrual cycles should be done. If they undergo torsion or rupture, which follows by acute abdominal pain and tenderness, surgical intervention is required.

Lutein cyst is less common and account for 5% of all ovarian tumors. It develops from the corpus luteum, when it grows larger than 3 cm, and fails to regress after 14 days. Sometimes lutein cyst can be

complicated by hemorrhage within the cyst, resulted from invasion of the ovarian vessels into the cystic cavity 2-3 days after ovulation.

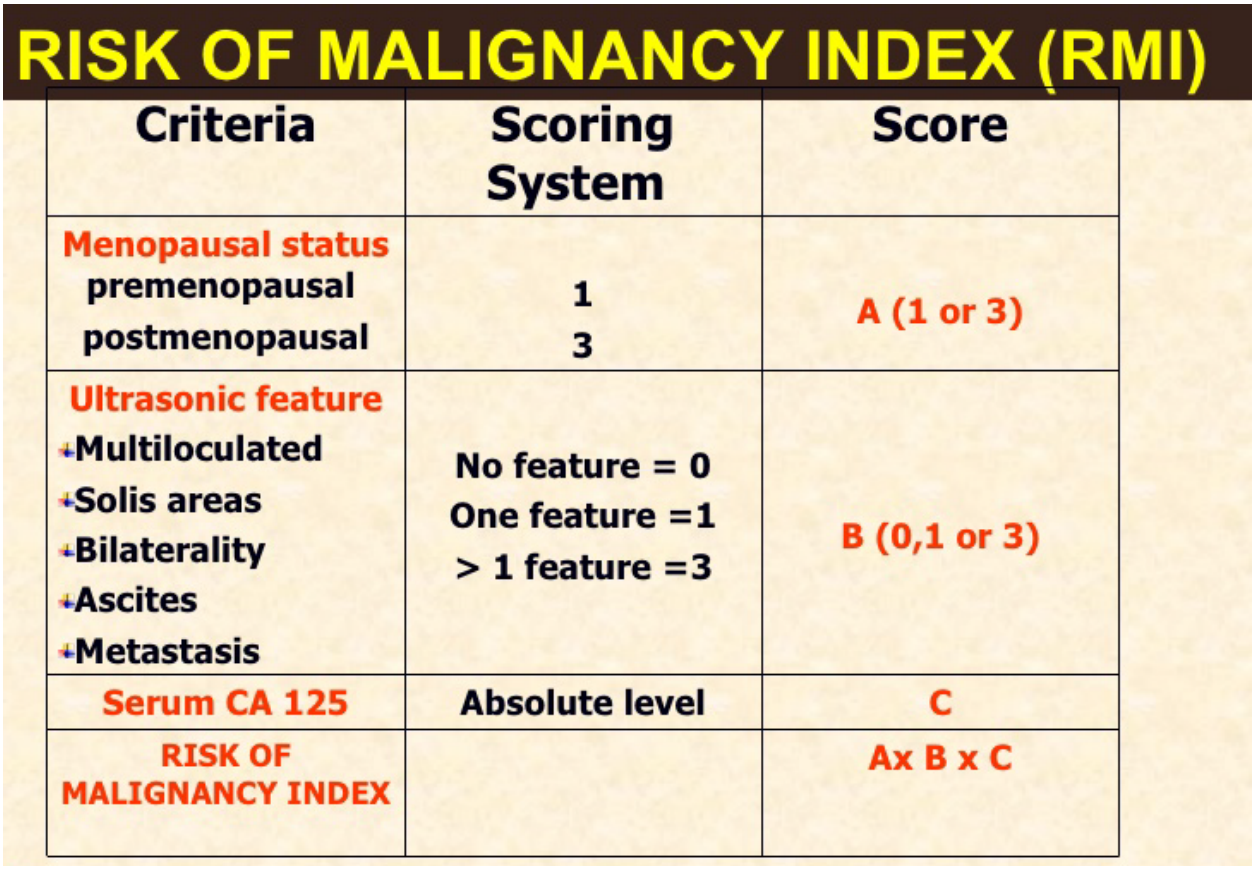
On one of the types of lutein cyst is theca-lutein cyst, associated with abnormally high blood levels of hCG or increased ovarian sensitivity to gonadotropins. The main risk factors for the developing of theca-lutein cysts are hydatidiform mole, stimulation of ovulation with gonadotropins or clomiphene, chorioncarcinoma, multifetal pregnancy. Another related benign condition of the ovaries is luteoma of pregnancy. It develops as e result of prolonged hCG stimulation of theca-cells during pregnancy. Luteoma of pregnancy resolves several weeks postpartum. They are commonly asymptomatic, but in 30% of cases cause maternal virilization, or ambiguous genitalia in a female fetus.

Lutein cysts are usually asymptomatic, bilateral, with solid consistence. Diameter of these cysts usually does not exceed the size of a chicken egg, but sometimes, especially as a result of stimulation by gonadotropins, cyst can become so extensive (>30 cm), that may cause ascites and systemic fluid imbalance. As lutein cyst produce progesterone they may cause delayed menstruation.

Diagnosis confirmed by pelvic ultrasound. Differential diagnosis is PCOS, ectopic pregnancy, malignant ovarian neoplasms, adnexal or pelvic abscess.

In premenopausal and postmenopausal patients diagnosis of lutein cysts should include determination of CA-125 and calculation of the

risk for malignancy index (RMI), due to their high malignancy potential. (Table 7.3-1)



RISK OF MALIGNANCY INDEX (RMI)

Criteria	Scoring System	Score
Menopausal status premenopausal postmenopausal	 1 3	A (1 or 3)
Ultrasonic feature Multiloculated Solis areas Bilaterality Ascites Metastasis	No feature = 0 One feature =1 > 1 feature =3	B (0,1 or 3)
Serum CA 125	Absolute level	C
RISK OF MALIGNANCY INDEX		Ax B x C

Figure 7.3-1 Risk of malignancy index = A x B x C

For small asymptomatic cysts observation within several menstrual cycles should be done. For treatment of abnormal menses and for preventing of new cysts formation, administration of oral contraceptives is favorable. If lutein cysts cause the pain, enlarge in size, has a complications such as a torsion, hemorrhage, or there are increased indicators of CA-125 and RMI, then surgical cystectomy is indicated.

Benign neoplastic ovarian tumors

Benign neoplasms of the ovaries are separated according to the most probable tissue of their origin: surface epithelial (65%), germ cell (15%), sex cord-stromal (10%), metastatic tumors (5%), miscelanous. WHO's Histologic Classification of ovarian tumors is presented in a Table 7.3- 2. They include benign, low-malignant, potential/borderline and malignant subtypes. The incidence of ovarian neoplasms starts increasing in the third decade, and progressively increases to peak in the seventh decade.

- **Surface epithelial - stromal tumors**
  - **Serous tumors:**
    - Benign (cystadenoma)
    - Borderline tumors (serous borderline tumor)
    - Malignant (serous adenocarcinoma)

  - **Mucinous tumors, endocervical-like and intestinal type:**
    - Benign (cystadenoma)
    - Borderline tumors (mucinous borderline tumor)
    - Malignant (mucinous adenocarcinoma)

  - **Endometrioid tumors:**
    - Benign (cystadenoma)
    - Borderline tumors (endometrioid borderline tumor)
    - Malignant (endometrioid adenocarcinoma)

  - **Clear cell tumors:**
    - Benign
    - Borderline tumors
    - Malignant (clear cell adenocarcinoma)

- **Sex cord - stromal tumors**
  - **Granulosa tumors:**
    - Fibromas
    - Fibrothecomas
    - Thecomas
  - **Sertoli cell tumors:**
    - Leydig cell tumors
  - Sex cord tumor with annular tubules
  - Gynandroblastoma
  - Steroid (lipid) cell tumors
- **Germ cell tumors**
  - **Teratoma:**
    - Immature
    - Mature
    - Solid
    - Cystic (dermoid cyst)
  - Monodermal (e.g., struma ovarii, carcinoid)
  - Dysgerminoma
  - Yolk sac tumor (endodermal sinus tumor)
  - Mixed germ cell tumors
- **Malignant, not otherwise specified**
  - **Metastatic cancer from nonovarian primary:**
    - Colonic, appendiceal
    - Gastric
    - Breast

Table 7.3-2 WHO histological classification of ovarian tumors

Epithelial ovarian tumors

Epithelial ovarian tumors by incidence are the most common ovarian neoplasms. These tumors derived from the mesothelial cells lining the peritoneal cavity and also lining the surface of the ovaries. They usually found in post-menopausal women, so the average age for epithelial neoplasms 60-65 years.

Common epithelial tumors are divided into five main categories according to the type of cells into which they differentiate:

-serous tumors, whose cells resemble those of the fallopian tube

-mucinous tumors, whose cells resemble those of the endocervix

-endometroid tumors, whose cells resemble those of the endometrium

-clear-cell tumors, whose cell resemble those of endometrial epithelium during pregnancy

-Brenner tumors, which cells are urothelial in appearance

There are also mixed forms that are rare.

The serous tumors are usually monolateral (90%), with smooth surface and elastic consistence .Size of these tumors may vary. About 70% of all serous tumors are benign, 5-10% has borderline malignant potential, and 20-25% is malignant. Sometimes serous cystadenoma may have a peduncle and undergo torsion.

Papillary cysts are often multilocular, have abnormal shape. On the walls of individual cells there is evidence of papillary proliferation, which have appearance of a cauliflower or coral. Multiple small

papillas give the surface of the cyst appearance of velvet. This kind of tumors is potential malignant.

The mucinous neoplasms are usually monolateral, multilocular, have spheric or oval shape with thick walls. They can reach huge size. Generally mucinous tumors are benign, but may be complicated by pseudomyxoma peritonei. They are filled by slimy liquid –pseudomucin.

The Brenner tumor is a small, smooth solid ovarian tumor with a large fibrotic component that resembles transitional cells of the bladder. They are usually benign and associated with mucinous epithelial elements.

Epithelial tumors are usually asymptomatic, unless they significantly enlarge, or undergo torsion or rupture. Patients complain on dull pain of different degree of severity in the lower abdomen, irradiating to the back and lower extremities. Pain may follow by dysuria, bloating and abdomen enlargement. They are not associated with a menstrual cycle. When neoplasms undergo torsion or rupture spontaneously, peritoneal irritation occurs. The cysts may rupture occasionally during or after a bimanual examination or sexual intercourse. Tumors also can undergo infarction. In case of complete infarction there can be abdominal rigidity and paralytic ileus. Sometimes epithelial tumors followed by menstrual dysfunctions.

Bimanual examination, pelvic ultrasound, CT, and MRI are helpful in diagnosis of ovarian neoplasms. Color Doppler helps in differentiation of benign and malignant tumors, as a malignant one have active vascularization. Determination of CA-125 and calculating of RMI are necessary in differentiation between benign and malignant tumors,

especially in postmenopausal patients. Diagnostic laparoscopy is helpful in distinguishing between the types of ovarian neoplasms and differentiation with other reproductive or pelvic organs pathologies.

Sex cord-stromal ovarian neoplasms

Sex cord-stromal neoplasms account for about 6% of all ovarian tumors. They are derived from the sex cord and stromal components of the developing gonads, and include fibromas, granulesa-theca cell tumors, and Sertoli-Leydig cell tumors. The most common is the fibroma that accounts for 4% of all ovarian tumors. Fibroma is composed entirely of fibroblasts forming collagen, has solid consistency, spheric or oval shape with smooth or rough surface. It is not hormonally active. Sometimes fibroma is associated with ascites caused by the transudation of fluid from the ovarian fibroid. When this ascetic fluid flows through the transdiaphragmatic lymphatics into the right pleural cavity, Meigs' syndrome develops, which is manifested by combination of ascites, hydrathorax and anemia. Usually develops in pre- or postmenopausal women, average age group 40-60 years. In 95% of cases they are unilateral.

Next in frequency is the granulesa-cell tumor, which composed almost exlusively of granulesa cells, but more commonly contains theca cells, lutein cells, or fibroblasts as well. They are functional. Granulosa cell tumors have been divided into adult and juvenile forms, which differ in their age distribution and morphologic features. Clinical manifestation of the granulosa cell tumors depends on their hormonal activity and has variety of signs and symptoms. For juvenile forms it is characteristic

precocious puberty, which followed by irregular bloody discharge from the vagina and moderate development of secondary sexual characteristics. In the reproductive age dysfunctional menstrual bleedings, anemia, endometrial hyperplasia, breast tenderness and fluid retention is characteristic. In postmenopausal women due to estrogen secretion postmenopausal bleedings and signs of rejuvenation may occur.

Granulesa cell tumors are usually benign (80%). Malignant tumors characterizes by metastasis to the parietal peritoneum, omentum, and serous layer of the abdominal organs.

Diagnosis is confirmed according to the clinical signs, pelvic examination and laboratory findings (hormones, CA 125), pelvic transvaginal ultrasound with or without color Doppler, and diagnostic laparoscopy.

Sertoli-Leydig cell tumors are composed of cells resembling Sertoli cells, Leydig cells, and fibroblasts in various combinations and degree of differentiation. Incidence of these tumors is less than 0.5% of all ovarian tumors. Sertoli-Leydig tumors are usually unilateral, confined to the ovaries. They are commonly characteristic for the second and third decade of life. These tumors contain a testicular structure that produces androgens. That’s why Sertoli-Leydig cell tumors are responsible for virilizing effects, such as hirsutism, temporal baldness, deepening of the voice, clitoromegaly, and change of the body to the masculine build. Around 50% of cases come to clinical attention because of progressive defeminization. About 19% of Sertoli-leydig tumors are malignant.

Germ cell tumors

Germ cell tumors account for 20-25% of all ovarian neoplasms, with the great majority presented by mature cystic teratoma or dermoid cyst Germ cell neoplasms can occur at any age. About 60% of these tumors occur in infants and children. Germ cell tumors develop from the primary sex cells of embryonal gonads and their derivatives, three germ layers: the endoderm, ectoderm, and mesoderm.

The most common germ cell neoplasm is cystic teratoma. Ovarian teratomas are a complex group of tumors that have been subdivided into three major categories: immature, mature, and monodermal and higly specialized. Immature teratomas contain at least some immature elements, most often neuroectodermal. Mature teratomas are composed exlusively of mature tissues. This tumor is so designated because its principal component in the great majority of cases is cutaneous epithelium with underlying elements derived from all three germ layers. This is slow growing tumor, diagnosed in women between 20-25 years. They are so called dermoid cysts. (Figure 7.3-1) Most commonly they composed of ectodermal tissue, such as sweet and sebaceous glands, hair follicles, teeth. Other tissue components of the dermoid cysts are mature brain, cartilage, bone tissue, thyroid, and bronchus and carcinoid cells. Dermoid cysts are not hormonal active. In almost 25% of the cases and particulary in older women, dermoid cysts undergo a secondary malignant change.

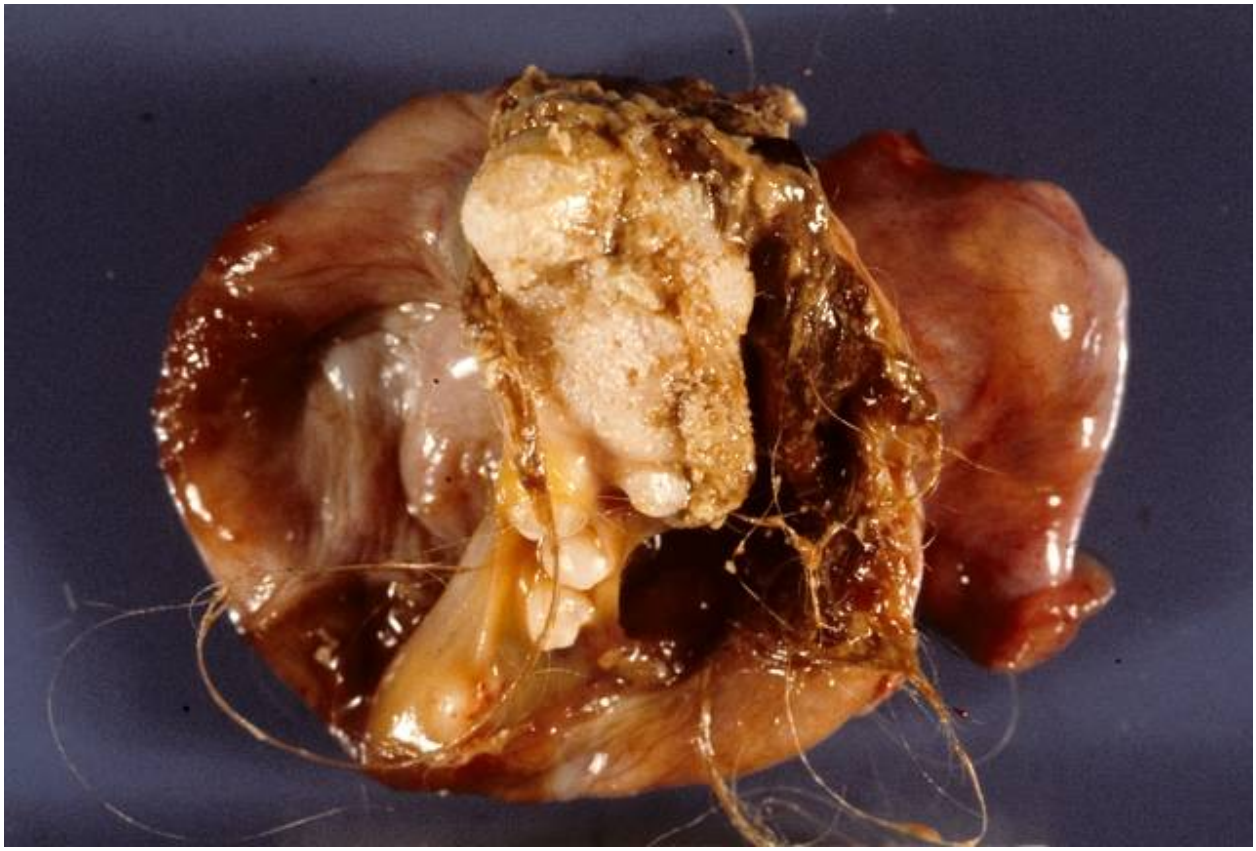


Figure 7.3-1 Appearance of a cut-open dermoid cyst

The most common type of the monodermal and highly differentiated teratomas is the struma ovarii, or thyroid tumor of the ovary.

Another kind of a germ cell tumor is dysgerminoma. It is malignant tumor of the ovaries. Incidence of dysgerminoma is 1-2% of all ovarian tumors. It is usually develops in teenagers and young women with genital infantilism and delayed menarche. It is prone to expansive growth, metastatic dissemination and germination to the neighbor organs.

Clinical signs of the germ cell tumors are the similar to those in other ovarian neoplasms.

Treatment of ovarian neoplasms

Treatment of ovarian neoplasms is surgical intervention. The definitive treatment depends on the type of the tumor, the patient's age, and her desire for preserve fertility.

Benign epithelial ovarian tumors are usually treated by unilateral salpingo-oophorectomy. Evaluation of the tumor should be done. The contralateral ovary must be carefully inspected to exclude bilateral lesion. If the patient is young and nulliparous and the neoplasms are benign and unilocular without excrements within the cyst, an ovarian cystectomy may be performed. High malignant potential and bilateral ovarian neoplasms in postmenopausal women are indications for hysterectomy with bilateral salpingo-oophorectomy.

Stromal cell neoplasms are generally treated by unilateral salpingo-oophorectomy. But the type of surgical intervention depends on the size of the neoplasm, patient's age and following gynecological and extragenital disorders.

Benign mature teratomas are treated by ovarian cystectomy with carefully inspection of other ovary, as teratomas in 20% of cases are bilateral. Immature teratomas are treated by hysterectomy with bilateral salpingo-oophorectomy with subsequent complex chemotherapy, because these tumors are malignant.

For dysgerminomas total hysterectomy with further radiotherapy is a treatment of a choice.

Chapter review

1. For treatment of postmenopausal bleeding it is necessary to perform diagnostic curettage of the uterus because:
   A) Endometrial hyperplasia
   B) Uterine mioma
   C) Absence of benefit from the hormonal therapy
   H) High frequency of dysfunctional bleedings
   I) High frequency of atrophic processes of endometrium
2. It is not one of the complications of uterine myomas:
   A) Regular menstrual cycle
   B) Torsion of the myoma
   C) Red degeneration
   D) Compression of the neighbor organs
   E) Menorrhagia
3. Which clinical sign is most common at submucosal myoma?
   A) Heavy menstruation
   B) Opsomenorhhea
   C) Compression of the neighbor organs
   D) Pain syndrome
   E) Amenorrhea
4. Which of the followings is characteristic feature of the myoma?
   A) Hormone depending benign tumor
   B) Develops from the skeleton muscle

C) Develops at puberty

D) Prone to malignization

E) Depend on menstrual cycle

5. Treatment of dermoid cyst is:

A) Surgical intervention

B) Administration of antibiotics

C) Observation

D) Physiotherapy

E) Hormonal therapy

6. The most effective method for diagnosis of ovarian neoplasms is:

A) Transvaginal ultrasound

B) laparotomy

C) MRI

D) Hysterosalpingography

E) Hysteroscopy

7. It is not used for diagnosis of the endometrium

A) Laparoscopy

B) Hysterosalpingography

C) Hysteroscopy

D) Endometrial Biopsy

E) Hydrosonography

8. Which kind of ovarian tumors is Meigh’s syndrome associated with?

A) Ovarian fibroma

B) Sertoli-Leydig cell tumor

C) Granulesa cell tumor

D) Mature ovarian teratoma

E) Follicular cyst

9. The following is a kind of true ovarian neoplasms:

A) Papillar cystadenoma

B) Follicular cyst

C) Lutein cyst

D) Paraovarian cyst

E) Inflammatory cyst

10. This is not a kind of epithelial ovarian tumor:

A) Mature tekoma

B) Serous cystadenoma

C) Mucinous cystadenoma

D) Cystadenocarcinoma

E) Brenner tumor

Chapter 8 Endometriosis and Adenomyosis

Endometriosis

Endometriosis is benign pathological condition of spreading and developing of the endometrial stroma and glands outside the uterine cavity. These are so called endometrial ectopies or heterotopies.

The term “endometriosis” was introduced in the scientific literature by B.Bell in 1892, but widespread recognition it received in the twenties of XX century after the publication of a series of fundamental studies. The first person described adenomyosis in the medical literature was Rokitansky, in 1860.

Endometriosis is one of the most common diseases of the female reproductive organs. The incidence of endometriosis among the women of age 20-40 years is 7-15%. At least one third of women with chronic pelvic pain (40-60%), and a significant number of infertile women (20-30%) have visualized signs of endometriosis. Occasionally endometriosis may occur in infancy, childhood, adolescence, but in these cases it usually associates with obstructive congenital abnormalities of the reproductive organs. After menopause endometriosis usually regresses. It shows that endometriosis is hormonal depending condition.

Endometriosis has a number of characteristics which distinguish it from other benign diseases: recurrence, similar to regularity of the ovarian-menstrual cycle, absence of the connective tissue capsula, propensity to infiltrative growth, due to enzymatic activity of the endometrial heterotopies, ability to metastasis.

Endometriosis is respond to cyclic to hormonal fluctuations in much the same way as intrauterine endometrium, with proliferation, secretory

activity, and cyclic sloughing of menstrual material. The implants proliferate under estrogen stimulation and slough with involution of the corpus luteum to the end of the second phase of menstrual cycle. The sloughed materials, which are metabolic active and followed by cyclic release of cytokines and prostaglandins, induce a profound inflammatory response resulting in pain and fibrosis.

The pathogenesis of endometriosis is not completely understood and remains a subject of the debates. There are several hypotheses that explain the occurrence of endometriosis:

1. The coelomic metaplasia theory proposes that the ovaries and mullerian ducts are the derivatives of the coelomic epithelium which may transfer by metaplasia to the endometrium under the influence of certain generally unidentified stimuli. The attractiveness of this theory is probability to explain the developing of endometriosis in the absence of menstrual function.
2. The lymphatic spread theory suggests that endometrial cells from the damaged at menstruation vessels of the uterus are taken up into the lymphatics draining and transported to the various organs and tissues. Microvascular studies demonstrated flow of lymph from the uterine body into the ovary, rendering possible role for the lymphatic system in the etiology of ovarian endometriosis.
3. The implantation theory is based on the assumption that during menstruation the endometrial fragments retrogradely transported through the fallopian tubes, implant and grow in various sites of abdominal cavity. The following arguments show the probability of this theory: menstrual reflux is universal process , which occur

in women even with intact fallopian tubes, localization of the endometrial islands close to the distal parts of the fallopian tubes, pelvic endometrial cells are viable and prone to proliferation, endometrium produces angiogenic factors that necessary for the vascularization, and evidence of endometrial heterotopies of the intact peritoneum during the laparoscopy in 20% of cases in practically healthy women.

A more recent proposal suggests extrauterine stem/progenitor cells originating from the bone marrow may differentiate into endometric tissue. Candidate cell lineages include bone marrow, mesenchymal stem progenitors, and endothelial progenitors, and this represents an active area of investigations.

Hereditary predisposition clearly plays role in pathogenesis of endometriosis. Hereditary or acquired properties of the endometrium and defects of the peritoneal epithelium, defective immune clearance of sloughed endometrium are also areas of active investigation in the search of the endometrial origin of the pathogenesis of endometriosis.

Collectively, investigations involving the pathophysiology of endometriosis have revealed several well supported molecular hallmarks of this desease:

1. Genetic predisposition
2. Estrogen dependence
3. Progesterone resistance
4. inflammation

Most authorities believe that several factors are involved in the initiation and spread of endometriosis. But there are some fundamental questions as, why only 10-15% of women have endometriosis when retrograde menstrual flow is universal almost for all women; why affected women have different degrees of severity of endometriosis? The immunologic response of women is appeared to be critical in pathogenesis of endometriosis.

The most common sites of involvement at endometriosis are: ovaries, posterior cul-de-sac, broad ligament, uterosacral ligament, rectosigmoid colon, bladder, distal ureter, rectovaginal septum. Endometriosis is occasionally seen in laparotomy scars as a result of spread of the endometrial tissue into the surgical incision. The lesions are clearly visualized during laparoscopy. (Figure 8-1)

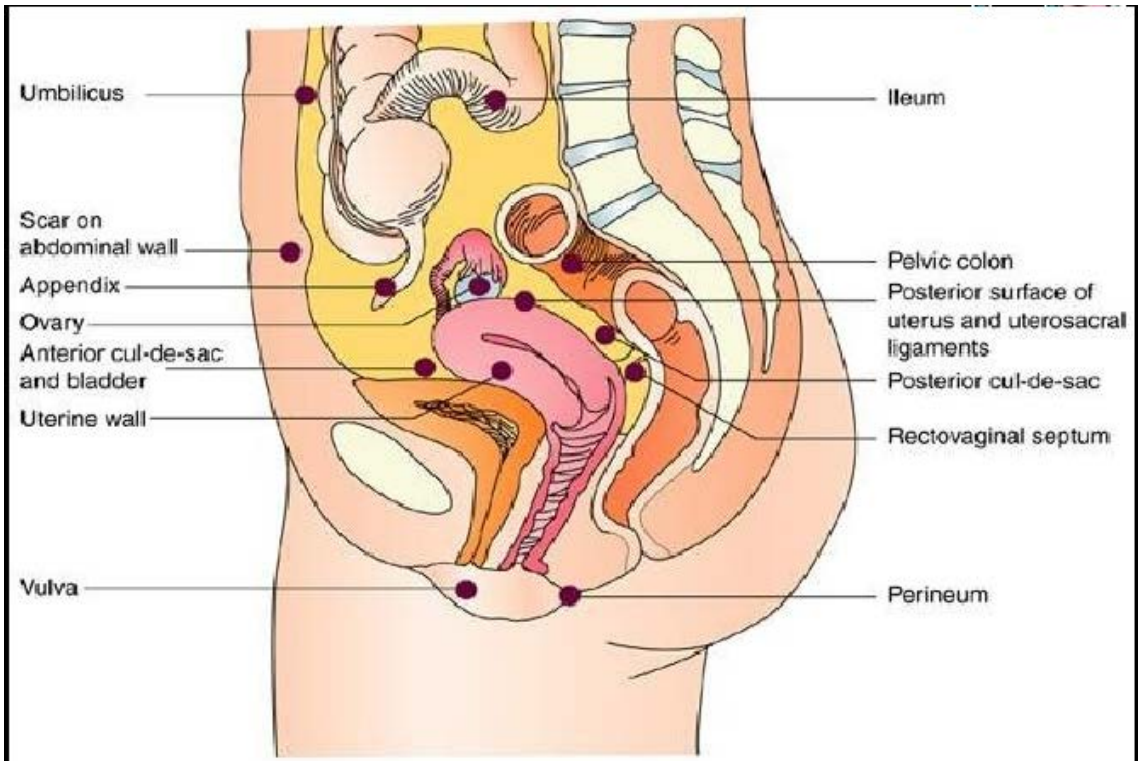


Figure 8-1 Common cites of endometriosis

The endometric implants typically has appearance of bluish gray, dark brown, or black “powder burn” lesions. Fibrotic scarred areas are yellow of white. The colour is attributed to hemolyzed blood from ectopic endometrium that is encapsulated by adhesions or fibrotic tissue. These lesions range in size and form a few millimeters to 2 cm in diameter and often are surrounded by various degree of fibrosis that may confer a puckered appearance. Newer lesions tend to be red, blood-filled active lesions. Older lesions tend to be much less active hormonally, scarre and blue-gray in color with a puckered appearance. All types of implants may coexist within the same patient. (Figure 8-2)

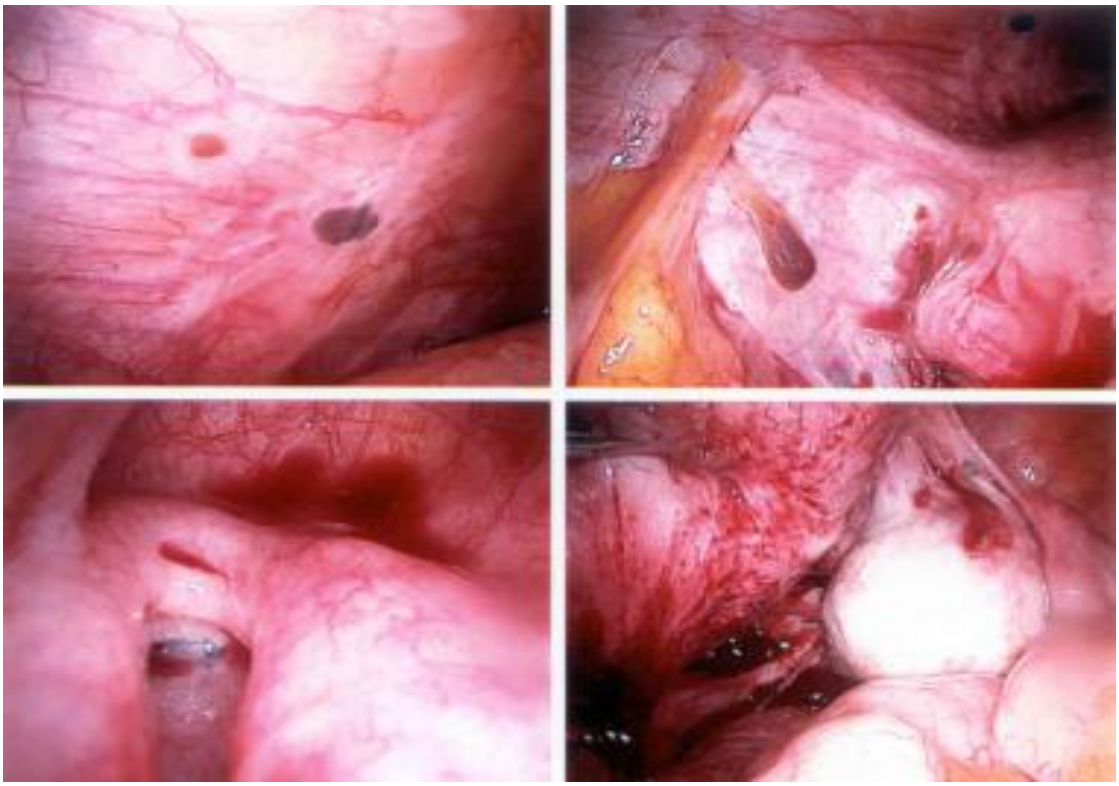


Figure 8-2 Appearance of endometriosis at the time of laparoscopy

Endometriosis implants may infiltrate subserosally and become deeply invasive and nodular. Endometriotic cysts typically are encountered in the ovary. After a cyst forms, cyclic hemorrhage within the cyst adds to the contents, causing cyst growth because of the slow reabsorption of debris. These endometriomas are called chocolate cysts, because filled with thick, chocolate- colored fluid that sometimes has the black color and tarry consistency of crankcase oil. (Figure 8.1-3) Microscopically, endometrial glands and stroma are present in the cystic wall. Hemorrhage into surrounding tissue may result in a zone of hemosiderin-laden macrophages or pseudoxantoma cells in addition to fibrosis. As intracystic pressure increases, endometriomas has tendency to perforate.

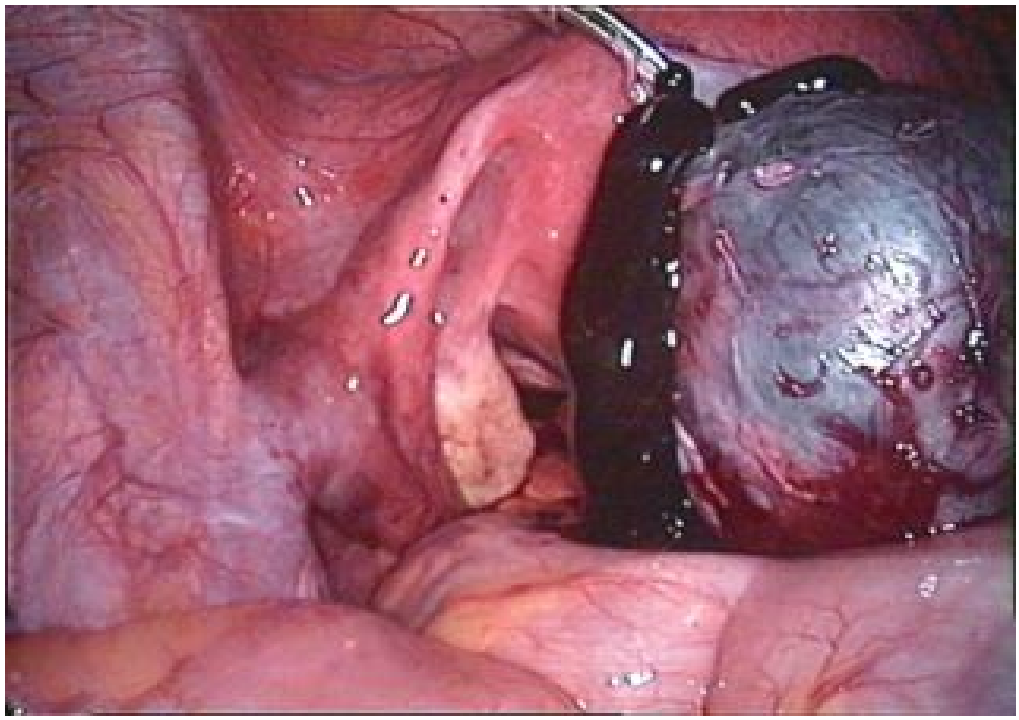
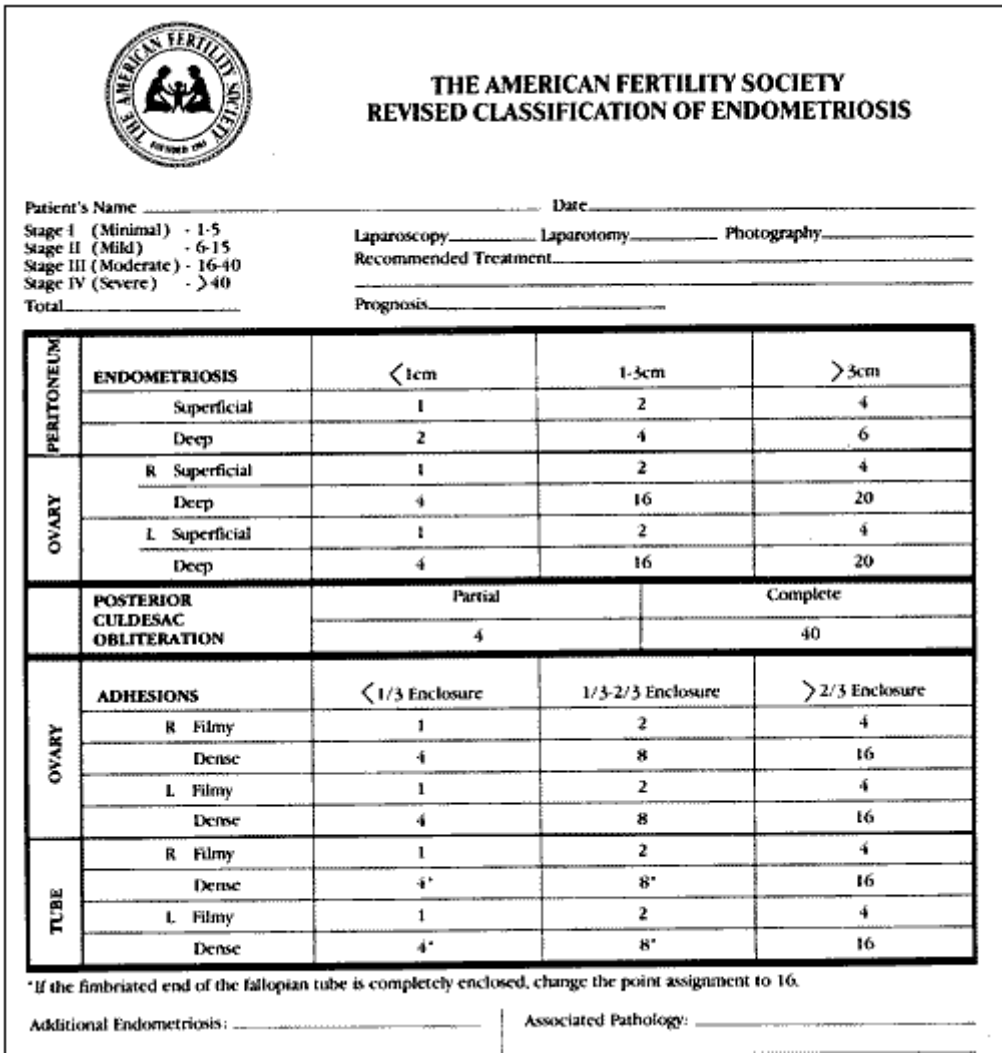


Figure 8-3 Typical ovarian endometrioma or “chocolate cyst”

There are a lot of classifications of endometriosis proposed during last 50 years. But the most common classification of endometriosis is

classification proposed by American Society of Reproductive Medicine, which is based on laparoscopic findings. It is include a description of the color of the lesions and the percentage of surface involved in each lesion type, as well as a more detailed description of any endometrioma. (Table 8-1)



THE AMERICAN FERTILITY SOCIETY
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

PERITONEUM	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial		Complete
		4		40
OVARY	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____ Associated Pathology: _____

Table 8-1 American Fertility Society classification of endometriosis

But this classification doesn't reflect the degree of infiltration at deep infiltrating process. One of the attempts to improve this case is ENZIAN Score (Table 8-2)

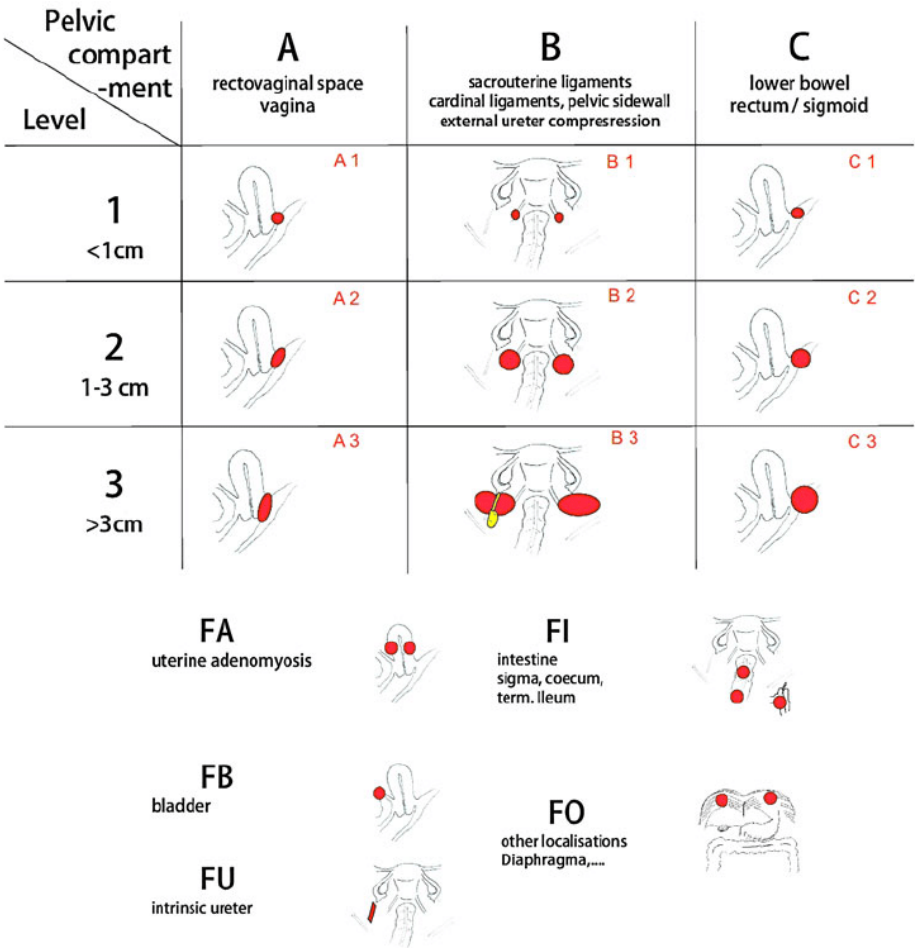


Table 8-2 ENZIAN scoring system for classification of endometriosis by degree of infiltration

There are two types of genital endometriosis: internal and external. Internal endometriosis implies lesions occurring in the uterine body and the cervix. External genital endometriosis is developing of lesions on the fallopian tubes, ovaries, utero-sacral and broad ligaments, peritoneum and cul-de-sac. Endometriosis of other organs and tissues is so called extragenital endometriosis.

Clinical manifestation of endometriosis is depending on localization, duration of the disease, following diseases, relation to the fertility state.

Endometriosis characterizes by recurrent duration. The main characteristic symptoms are pain and infertility. The characteristic triad of pain syndrome associated with endometriosis is dysmenorhhea, dyspareunia, dyschezia. Pain syndrome at endometriosis occurs gradually and depends on the menstrual cycle, starting 1-2 days before estimated menstruation and resolving at the end of the menses. This cyclic pain is related to the premenstrual swelling and extravasation of blood, which induce an intense inflammatory reaction. Deep infiltrated lesions, especially those in the cul-de-sac, isthmic part of the uterus, sacro-uterine ligament are associated with more severe pain. Menstrual dysfunction as heavy and prolonged menstruation is more evident. The characteristic symptom is dark bloody discharge 2-5 days before and after menstruation.

Allen-Masters syndrome-is a pain syndrome associated with developing of tissue defects over the posterior sheet of broad ligament as a result of external endometriosis. Clinical signs are the same as at external endometriosis, and laparoscopy is the only way for differentiation.

Dyspareunia occurs when the cul-de-sac, uterosacral ligament, and portions of posterior vaginal fornix are involved to the pathological process. Dyschezia is experienced with uterosacral, cul-de-sac, and rectosigmoid colon involvement.

There is no clear relationship between the stage of endometriosis and the frequency and severity of pain syndrome.

Most probable causes of infertility associated with endometriosis are:

-tubal occlusion as a result of adhesions and scarring of the tubal cavity due to endometrial lesions

-peritoneal infertility, as a result of adhesions

-endocrine infertility as a result of hormonal imbalance and elevation of prolactin level associated with endometriosis

-immune reactions associated with inhibition of blastocyst implantation and deactivation of sperm by macrophages.

Incidence of spontaneous pregnancy decreases with increasing of disease severity. According to ENDOCAN, cumulative indicator of spontaneous pregnancy in patients with endometriosis is 15.7%

To get diagnosis of endometriosis may take some time. The symptoms of endometriosis are very similar to other common conditions. The main differential diagnosis in the acute phase of endometriosis is chronic pelvic inflammatory disease, acute salpingitis, hemorrhagic corpus luteum, benign or malignant ovarian neoplasms, and ectopic pregnancy.

A complete history and physical examination, including speculum and bimanual examination, may aid in diagnosis. The diagnosis of endometriosis should be suspected in an afebrile patient with the pelvic pain, presence of focal tenderness or nodularity of the uterosacral ligaments or the cul-de-sac on bimanual examination. An enlarged, tender, cystic mass may suggest an endometrioma. As the physical examination has poor sensitivity, specificity, or predictive value in the diagnosis of endometriosis, the radiologic examination, including transvaginal ultrasound and MRI, is used.

Patients with endometriosis have elevated blood levels of CA 125. But this test is not specific, as it also increases in the other pathological conditions as ovarian cancer, pregnancy, menstruation, pelvic inflammatory diseases, and doesn't reflect the severity of endometriosis.

The only definitive method of diagnosis of endometriosis is laparoscopy. The laparoscopic visualization of peritoneal lesions alone is of limited accuracy, and if a diagnostic laparoscopy is performed, confirmatory biopsies of peritoneal lesions, even atypical ones, will be of value. Only 54-67% of suspected endometriotic lesions are confirmed histologically. Histopathologic diagnosis of endometriosis requires the presence at least of two of these histologic features: endometrial gland, endometrial stroma, endometrial epithelium, and hemosiderin-laden macrophages.

Treatment for endometriosis, as medical treatment, non-pharmocological treatment as well as surgery, is indicated in presence of pain syndrome and infertility due to endometriosis.

Medical treatment is targeted toward reducing pelvic pain, dyspareunia, dysmenorrhea, abnormal menstrual bleeding and risk for disease progression. Initial treatment of suspected endometriosis includes administration of progestins, danazol, extended-cycle combined oral contraceptives, nonsteroidal anti-inflammatory drugs, and gonadotropin –releasing hormone (GnRH) agonists. The first-line treatment includes empiric therapy with NSAID, oral contraceptives and progestins. When an inadequate response occurs, second-line treatment with GnRH agonists, higher dose progestines, or danazol are effective.

Women with recurrent endometriosis who wish to preserve their fertility are treated with NSAID or oral contraseptives. If none of these therapies is sucsessful, progestins, GnRh agonists, and androgens may be used. Administration of levonorgestrel-releasing intrauterine device reduces pain syndrome and dysmenorrhea, induces the regression of cul-de-sac lesions, but adverse effects are common.

If fertility is not a concern, 6-9 months danazol therapy is used. Three years after cessation of danazol, 40% of patients have a recurrence of endometriosis. Adverse effect of danazol is elevation of blood level of free testosterone and associated with it signs of hyperandrogenia as hirsutism, acne, alopecia.

GnRH agonists are effective in treatment of endometriosis, but cause a temporary medical castration. The hot flashes, demineralization of bones, vaginal dryness, and unfavorable lipid profile are the most common side effects of GnRH agonists. If therapy with GhRH agonists is effective in reducing the symptoms of endometriosis, then add-back therapy with progestins or oral contraceptives is used. This therapy helps to restore estrogen deficiency without reducing the efficiency of GnRH agonists.

Surgical removal of lesions is indicated in patients who wish to preserve fertility. In this situation the main goal is to destroy all the endometriotic implants and remove all adhesions. Small lesions undergo excision or laser ablation, while large endometriomas require only surgical resection. Salpingoectomy with or without the ovary is indicated in case of tubal endometriosis.

Endometriomas are associated with an increased risk of torsion and rupture and should be removed. Resection of the ovary or total oophorectomy should be performed.

Definitive surgical treatment is appropriate in women who do not wish to preserve fertility and in whom conservative medical and surgical management have been unsuccessful. Hysterectomy with bilateral salpingo-oophorectomy is a treatment of a choice. In young women with normal ovaries, a hysterectomy with ovarian preservation should be considered.

Postoperative hormonal therapy is effective to prevent recurrence of endometriosis. Continuous oral contraceptives and levonorgestrel-releasing intrauterine device are attractive long-term options.

Endometriosis is recurrent disease. Inhibition or minimization of retrograde menstrual flow, reduction of estrogen stimulation and inflammatory reactivity in the pelvis can reduce the risk for endometriosis.

Adenomyosis

Adenomyosis is defined as the extension of the endometrial tissue into the myometrium. This is an incidental finding on pathologic examination when it is seen in up 60% of women in their 40s. (Figure 8-4) Adenomyosis is usually seen in women in reproductive age because its growth depends on estrogen stimuli. There was proved that

prevalence of adenomyosis has been correlated with increasing parity. About 23.8% of adenomyosis is followed by endometriosis of different degree of severity, superficial peritoneal lesions to deep infiltrating forms.

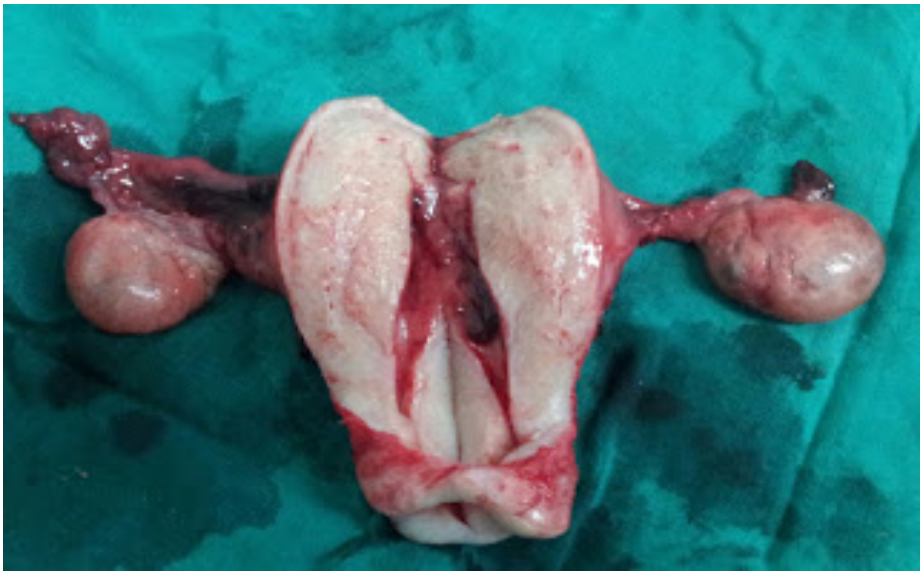


Figure 8-4 Cut-open enlarged uterus with signs of adenomyosis

There are several theories suggested as etiology of adenomyosis:

-extra tissue in the uterine wall present before birth that grow during reproductive period

-invasive growth of endometrial tissue to the damaged myometrium as e result of surgical interventions

-metaplasia of the stem cells presenting in the myometrium into the endometrial

-immune imbalance and decreasing of defending ability of endometrial tissue due to inflammatory processes

Histologically adenomyosis is classified to:

1. diffuse
2. nodular
3. sclerotic
4. cystic

Depending the degree of invasion of endometrial tissue into the uterine wall there are 4 stages of dissemination of pathologic process:

I pathological process bordered by the mucous layer

II pathological process reaches the mean uterine thickness

III all of the myometrium involved to the pathological process

IV in addition to the uterus, parietal peritoneum and pelvic organs are involved to the pathological process

The uterus affected by adenomyosis is enlarged with thickened myometrium containing characteristic glandular irregularities, with implants containing both glandular tissue and stroma. The endometrial cavity is also enlarged. (Figure 8-4)

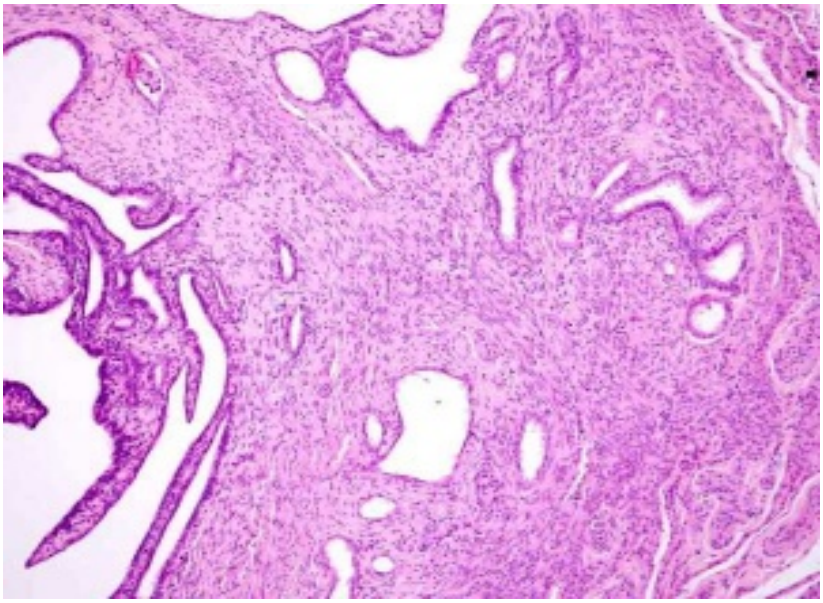


Figure 8-5 Histologic illustration of adenomyosis (endometrial glands and stroma)

Although many women are asymptomatic, adenomyosis may cause the following symptoms:

-dysmenorrhea

-heavy and prolonged menstrual bleeding

-dyspareunia

-abdominal pressure and bloating

Because of enlargement of the uterus, adenomyosis can cause problems with fertility.

If adenomyosis is suspected the first step is a physical examination. A pelvic examination reveals an enlarged uterus. Usually the uterus enlarges symmetrically, but occasionally it may enlarge asymmetrically, which make it very difficult to distinguish from the uterine myoma. If

bimanual examination is conducted premenstrually the uterus may be tender at palpation.

Radiologic imaging helps in diagnosis of adenomyosis. The sonographic findings of adenomyosis, best obtained by transvaginal echography, include the following:

-globular uterine enlargement

-cystic anechoic spaces or lakes in the myometrium

-uterine wall thickening

-subendometrial echogenic linear striations

-heterogeneous echo texture

-obscure endometrial/myometrial border

-thickening of the transition zone (layer that appears as a hypoechogenic halo surrounding the endometrial layer)

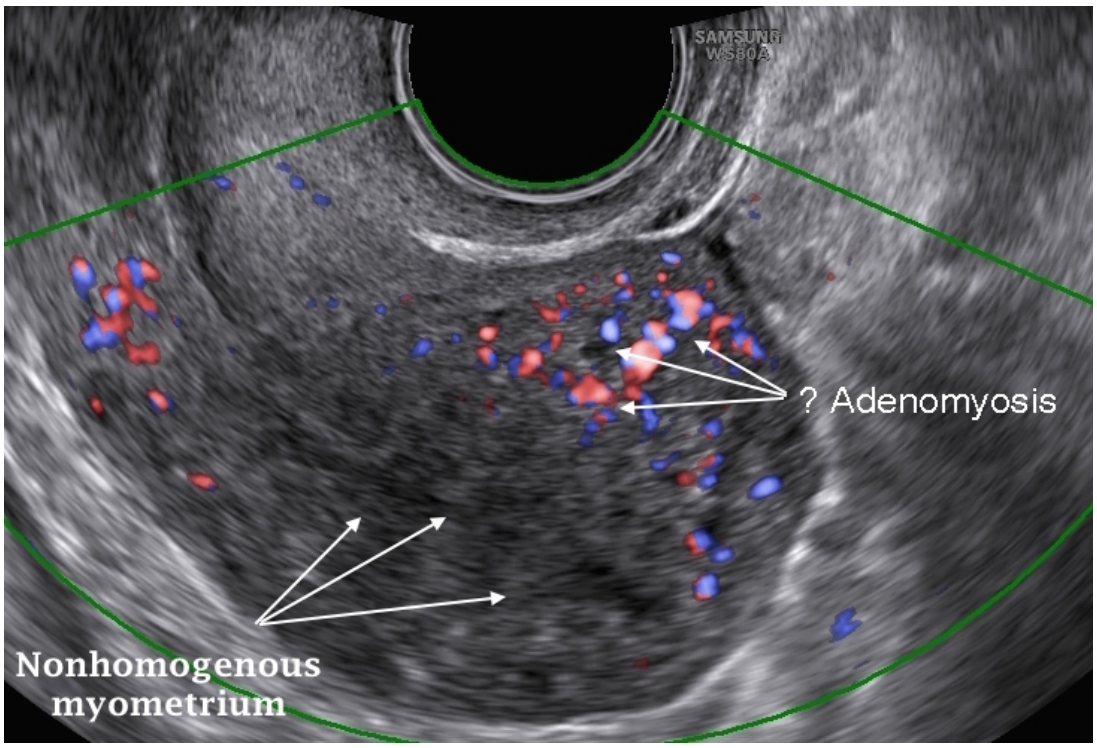


Figure 8-6 Ultrasound image of enlarged spheric shaped uterus with presumptive diagnosis of endometriosis

But its diagnostic sensitivity is still suboptimal, ranging from 50-87%. MRI is most effective in both diffuse and local adenomyosis. CT has poor diagnostic value due to similar images portrayed by foci and normal myometrium.

The treatment of adenomyosis is depends on the symptoms. Medical therapy with NSAID, combined oral contraceptives, progestins, levonorgestrel-containing intrauterine device for reducing of heavy menstruation and dysmenorrhea is the treatment of a choice for patients with adenomyosis. Latest researches show that administration of Bromocriptine and RU486 have been shown to suppress adenomyosis. Surgical treatment is indicated for the patients with absence of the effect of conservative therapy. Hysterectomy and endometrial ablation for bleeding control are the most common surgical interventions inducted in patients with adenomyosis. The uterine artery embolisation for treating adenomyosis is effective for symptom relief in a substantial proportion of patients who wish to preserve their fertility.

Chapter Review

1. What is the prevalence of endometriosis in reproductive age women?

A) 7-15%

B) 25-35%

C) 5-8%

D) 40%

E) 30-60%

2. The most common symptoms of endometriosis are:

A) Dysmenorrhea and dyspareunia

B) Amenorrhea

C) Heavy menstrualtions

D) Vaginal discharge

E) Uterine enlargement

3. What is the best imaging technique for diagnosis endometriosis?

A) Laparoscopy

B) Colposcopy

C) CT

D) Abdominal ultrasound

E) X-rays

4. These causes of pelvic pain associated with endometriosis:

1. Inflammatory factors

2. Scarring and retraction

3. Ascites

4. Purulent abscess

5. Compression and stretching

A) 1, 2, 5

B) 2, 4, 5

C) 1, 3, 4

D) 3, 4, 5

E) 1, 4, 5

5. Which of the following is the side effect of GnRH agonists?

A) Hot flashes and bone loss

B) Heavy menstruation

C) Hirsutism

D) Acne and alopecia

E) Increasing of prolactin level

6. The following is characteristic for Endometriosis:

A) Has recurrent duration

B) Followed by hyperandrogenia

C) Leads to chronic intoxication

D) Associated with hyperprolactinemia

E) Associated with uterine leyomyomas

7. Which medical treatment is preferable for treatment of endometriosis?

A) GnRH agonists

B) Antibiotics

C) Eubiotics

D) Glucocorticoids

E) Bromocriptine

8. What is the most common symptom of adenomyosis?

A) Abnormal uterine bleeding and dysmenorrhea

B) Amenorrhea

C) Purulent vaginal discharge

D) Acute pelvic pain

E) Infertility

9. What are the ultrasound characteristics of adenomyosis?

1. Solid formations of myometrium with well-defined capsula

2. Asymetrical enlarged uterus

3. Indistinct endometrial-myometrial boarder

4. Small anechoic lakes in the myometrium

5. Homogenous myometrial echotexture

A) 2, 3, 4

B) 1, 3, 5

C) 2, 3, 5

D) 3, 4, 5

E) 1, 2, 3

10. What is the treatment of choice for adenomyosis in patient with persistent symptoms?

A) Hysterectomy and endometrial ablation

B) Administration of combined oral contraceptives

C) Administration of NSAID

D) Curettage of the uterine cavity

E) Cryodestruction

Chapter 9 Cervical lesions

9.1 Etiology and Epidemiology

Cervical cancer is the 2nd most common cancer in women in both incidence and mortality. It kills about 275,000 women a year worldwide. About 80% of new cases reported each year occur in developing countries. Highest risk regions include Eastern and Western Africa,

South-Central Asia, South America and Caribbean. Rates are lowest in Western Asia, North America and Australia. Recent studies have identified a High-risk human papillomavirus as the cause of all cervical cancers, and according to the International Agency for Research on Cancer (IARC) cervical cancer may be the first human cancer to have a single necessary cause. In the 1970s, Dr. Harald zur Hausen found that specific types of HPV could be identified in the majority of invasive cervical cancers. For this research he was awarded by the Nobel Prize in Physiology or Medicine 2008.

There are 15 high-risk HPV types, and types 16 and 18 are responsible for 70% of cervical cancers. Types 6 and 11 are associated with cervical flat condylomas and low-grade cervical intraepithelial lesions. Flat condylomas were first studied by A. Meisels and R.Fortin in 1976. In 60% of cases they associated with dysplasia, in 5% of cases with preinvasive carcinoma.

Anatomic and physiologic features of the cervix in the different age periods are predisposing for developing of cervical lesions. So, the adolescent cervix, due to hormonal changes, is believed to be more susceptible to carcinogenic stimuli because of metaplastic processes within the transformation zone.

The majority of the cervix portio is covered by stratified squamous epithelium, so called ectocervix. Cervical squamous cells are divided into four distinct layers: basal, parabasal, intermediate, superficial. The endocervical canal is layered by a single layer of tall columnar cells. The majority of these cells produce mucus, but a few columnar cells are

ciliated and participate in sperm transport. The columnar epithelium has a red appearance because blood vessels in the underlying stroma are shown through it.

The intersection of the stratified squamous and columnar cells is known as the squamous-columnar junction (SCJ). The location of SCJ varies during the different periods of women lifetime and depends on hormonal activity. The transformation zone is defined as the area between the original SCJ and the new SCJ. Metaplasia is a transformation from one mature cell type to a different mature cell type. The process involves conversion from a columnar cell to a stratified squamous cell. (Figure 9.1-1)

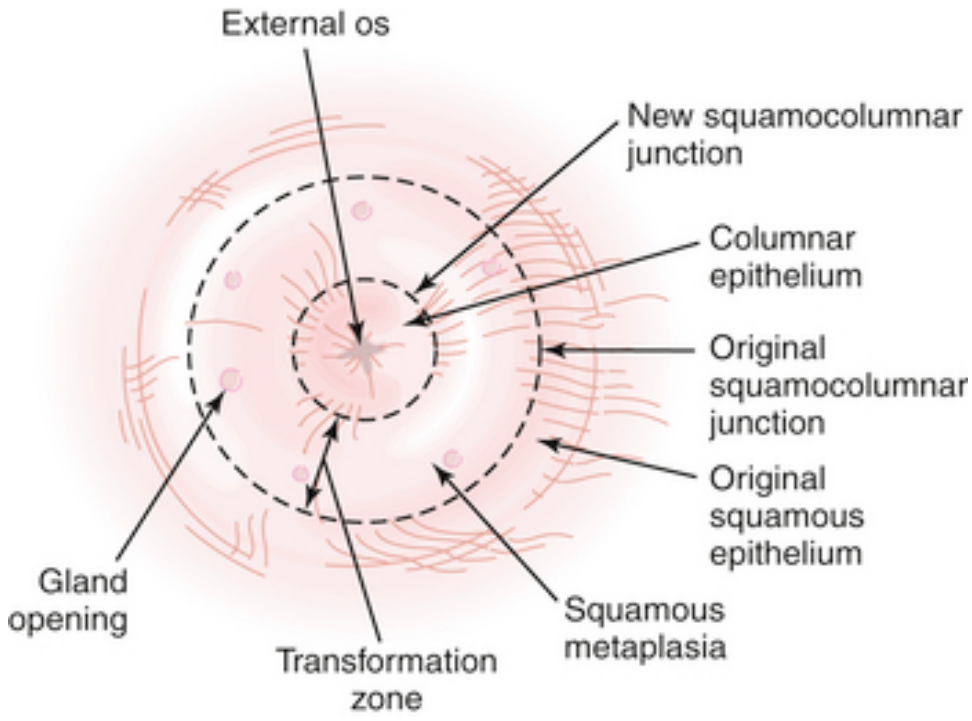


Figure 9-1 Schematic representation of the squamocolumnar junction and transformation zone

This squamous metaplasia is normally a physiologic process. Factors that induce squamous metaplasia in the cervix are still poorly understood but may include environmental conditions, mechanical irritation, chronic inflammation, pH changes, or changes in sex steroid hormone balance. When the cervix is affected by HPV, cellular alterations occur that result in an atypical transformation zone. These atypical changes initiate CIN, which is the preinvasive phase of cervical cancer.

Most cervical lesions are either latent or subclinical, and are detected on Pap smear. The median age of cervical cancer is 49, but older women remain at risk. There are the following risk factors for cervical cancer:

-early onset of sexual life

-multiple sexual partners

-young age at first pregnancy

-high parity

-lower socioeconomic status

-smoking

Virgins and women with limited sexual exposure were recognized to be at low risk.

Due to widespread availability of cytologic screening, incidence and mortality rates of cervical cancer are significantly reduced. Women who do not get regular screening with Pap smear are particulary vulnerable to cervical cancer. With annual cytologic screening, the lifetime risk drops to 0.3% from 3.7%.

The American College of Obstetrics and Gynecology has recommended that all women undergo an annual physical examination, including Pap smear, within 3 years of sexual intercourse, or by age 21. Both ectocervix and endocervical canal should be sampled when taking the Pap smear.

Two prophylactic vaccines are available for prevention of cervical lesions caused by HPV: quadrivalent vaccine Gardasil (protects against HPV types 6, 11, 16, 18), and bivalent vaccine Cervarix (against 16 and 18 types of HPV). Vaccination is most effective if performed before the onset of sexual life. In some countries HPV vaccination is included to the obligatory immunization program.

In 1991 and 2001 the Bethesda System for reporting cervicovaginal cytologic abnormalities was established. The 2001 Bethesda terminology calssifies a Pap test report as either negative for intraepithelial lesions or malignancy, or demonstrating an epithelial cell abnormality. Table 9.1 summarizes the Bethesda System currently in use.

Table 1

Bethesda Classification of Cervical Cytology

ADEQUACY OF THE SPECIMEN

Satisfactory for evaluation

Satisfactory for evaluation but limited by . . . (specify reason)

Unsatisfactory for evaluation . . . (specify reason)

GENERAL CATEGORIZATION (Optional)

Within normal limits

Benign cellular changes: See descriptive diagnosis

Epithelial cell abnormality: See descriptive diagnosis

DESCRIPTIVE DIAGNOSIS

Benign Cellular Changes

Infection

Trichomonas vaginalis

Fungal organisms morphologically consistent with *Candida* species

Predominance of coccobacilli consistent with shift in vaginal flora

Bacteria morphologically consistent with *Actinomyces* species

Cellular changes associated with herpes simplex virus

Other[a]

Reaction Changes

Reactive cellular changes associated with:

- Inflammation (includes typical repair)
- Atrophy with inflammation ("atrophic vaginitis")
- Radiation
- Intrauterine contraceptive device (IUD)
- Other

Epithelial Cell Abnormalities

Squamous cell

- Atypical squamous cells of undetermined significance: qualify[b]
- Low-grade squamous intraepithelial lesion (LGSIL) encompassing: HPV[a] mild dysplasia/CIN 1
- High-grade squamous intraepithelial lesion (HGSIL) encompassing: moderate and severe dysplasia, CIN 2, and CIN 3/CIS
- Squamous cell carcinoma

Glandular cell

- Endometrial cells, cytologically benign in postmenopausal woman
- Atypical glandular cells of undetermined significance: qualify[b]
- Endocervical adenocarcinoma
- Endometrial adenocarcinoma
- Adenocarcinoma, NOS

Other Malignant Neoplasms: specify

HORMONAL EVALUATION (Applies to Vaginal Smears Only)

Hormonal pattern compatible with age and history

Hormonal pattern incompatible with age and history: specify

Hormonal evaluation not possible due to: specify

CIN = Cervical intraepithelial neoplasia; CIS = Carcinoma in situ; NOS = Not otherwise specified

[a] Cellular changes of human papillomavirus (HPV) previously termed koilocytosis, koilocytotic atypia, and condylomatous atypia are included in the category of LGSIL.

[b] Atypical squamous or glandular cells of undetermined significance should be further qualified, if possible, as to whether reactive or premalignant vs malignant process is favored.

Table 9.1-1 Bethesda classification of Cytologic abnormalities of the cervix

There are also a variety of different benign conditions of the cervix, such as true cervical erosion, cervical ectropion, leukoplakia, cervical polyp, and Nabothian cycts.

Cervical erosion-defect of cervical epithelium exposing subepithelial tissue, detected in approximately 2% of women. Usually occurs as a result of inflammatory processes, trauma, chemical, electrical or laser burn, trophic due to radiotherapy or cancer.

A cervical ectropion is a condition when the columnar epithelium of the cervical canal extends to the surface of external portio of the cervix and can be visualized by speculum examination as a red, velvet-like area. It is a result of estrogen activity and most commonly it occurs in a young girls, during pregnancy and in women who intake oral contraceptives.

Then columnar epithelium undergoes squamous metaplasia, and transforms to stratified squamous epithelium. This tissue growth blocks the cervical crypts, trapping cervical mucus inside the crypts. So, mucus-filled cysts appear on the surface of the cervix. These are nabothian cysts. They are usually 2 to 10 millimeters in diameter, range in color from yellow to amber and have appearance of bumps on the cervical surface. (Figure 9.1-2)

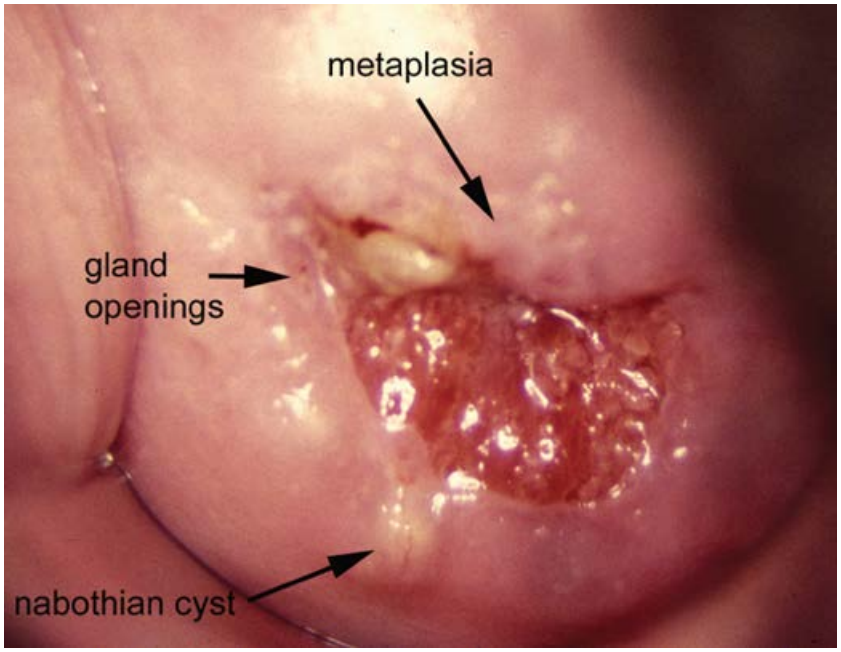


Figure 9.1-2 Nabotian cysts and gland openings at metaplasia zone

Leukoplakia is a hyperkeratotic cervical lesion. Clumps of keratotic, anucleate, squamous cells are the common cytologic findings. Leukoplakia has appearance of gray opaque patchy lesion. The cause of leukoplakia is not yet clear, but endocrine disorders, local irritation and dysplasia are suggested as predisposing factors for leukoplakia. It is

usually asymptomatic. (Figure 9.1-3)

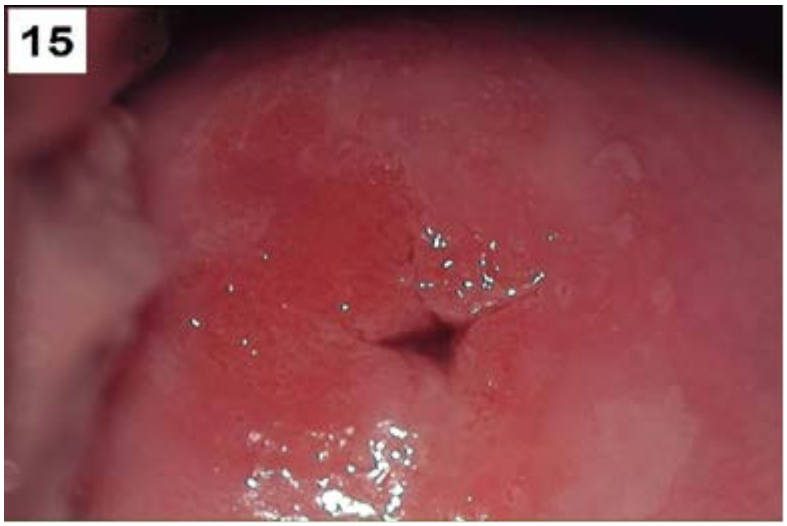


Figure 9.1-3 Cervical leukoplakia

Cervical and endocervical polyps are the most common benign neoplastic growths of the cervix. They have a narrow stalk and occur more often in premenopausal women. There are six different types of polyps: adenomatous, cystic, fibrous, vascular, inflammatory, and fibromatous. Incidence of malignization is 1%. Polyps are smooth, soft, reddish-purple to cherry red formations, may be single or multiple. Cervical polyps are usually asymptomatic, but may result in bleeding or spotting due to vaginal examination and sexual intercourse, and acyclic bleeding. Treatment consists of simple removal of the polyp and prognosis is generally good.

9.2 Cervical Intraepithelial lesions

Squamous intraepithelial neoplastic abnormalities, also reffered to a squamous dysplasia, are associated with the presence of HPV. CIN represents a spectrum of disease, ranging from CIN I (mild dysplasia) to CIN III (severe dysplasia and carcinoma in situ). About 35% of patients with CIN III develop invasive cancer within 10 years. Lower grades of CIN may regress spontaneously. The term cervical intraepithelial neoplasia was replaced by the term cervical intraepithelial lesions.

The degree of surface abnormality reflects the type of viral interaction with the immature squamous cell. In mild dysplasia, HPV produces proteins that direct the host cells to undergo maturation and cell death, resulting in exfoliating, disintegrating and releasing of a number of intact viral particles. In high degree dysplasia disruption of HPV DNA and integration to the host cell genome occur. Unregulated production of oncogenic viral proteins results in transformation and proliferation of the immature basal and parabasal cells that contain the viral DNA.

CIN is characterizing by abnormal epithelial maturation and proliferation above the basement membrane. A loss of the normal progressive cellular differentiation in the bottom thirds of the epithelial layer is characteristic for CIN I, or mild dysplasia. The cells in the upper two thirds of the epithelium may appear normal. In CIN II, or moderate dysplasia, the degree of proliferation among the basal and parabasal cells increases, and the layer of abnormal cells reach the upper third of the epithelial surface. In CIN III or severe dysplasia, the proliferation of immature cells involves almost the full thickness of the epithelium. (Figure 9.2-1)

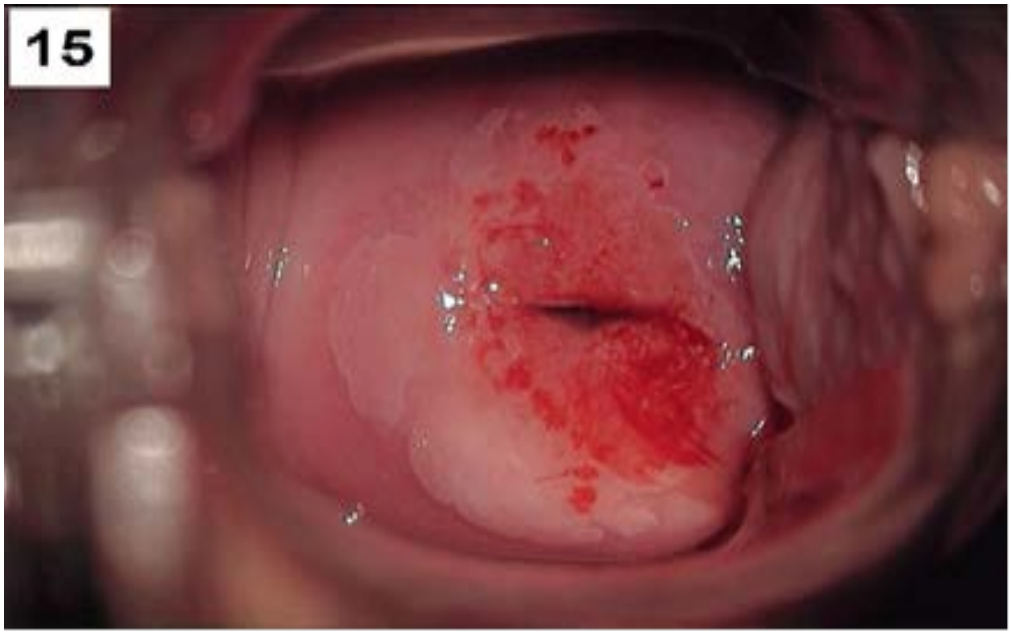


Figure 9.2-1 Cervical intraepithelial lesion grade III

Invasion is characterized by disruption of the basement membrane between the epithelial surface cells and the underlying stroma.

CIN is usually have asymptomatic duration and is found occasionally during colposcopy. Application of 3-5% acetic solution and Lugol's solution enhances the detection of neoplastic lesions during colposcopy. At colposcopy, the normal findings are squamous epithelium, which appears gray and homogenous, and the columnar epithelium, that has red color and grape-like appearance. The transformation zone can be identified by the presence of gland openings that are not covered by the squamous metaplasia. The color of metaplastic epithelium is paler in comparison with original squamous epithelium. Normal blood vessels look like a tree brunches.

Acetic acid has been used for the detection of precancerous cervical lesions. The pathologic area becomes acetowhite. The cause of acetowhitening is nuclear proteinprecipitation and increased light reflex from the areas of increased nuclear density. And as the metaplastic tissue has increased nuclear protein, it becomes whiter than the original squamous epithelium. The iodine in Lugol's solution transiently stains the glycogen in squamous cells, imparting a dark brown color to normal glycogenated epithelium. In contrast, most neoplastic tissues do not contain glycogen and, thus, do not stain. (Figure 9.2-2)

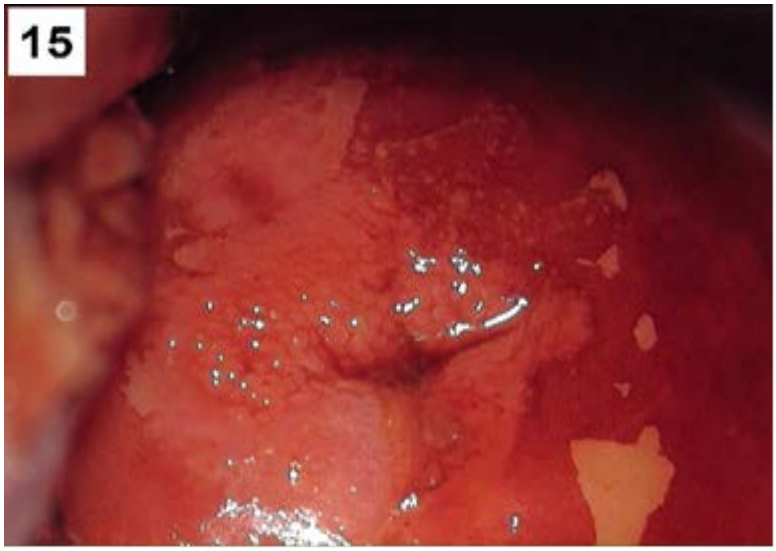


Figure 9.2-2 Negative Shiller's test: pathological areas didn't color by iodine solution

Two basic abnormalities in vascular pattern are characteristic for CIN: punctuation and mosaicism. Punctation is presented by single-looped terminal capillaries within stromal papillae of either original squamous epithelium or the transformation zone. These twisted vessels run perpendicularly or obliquely toward the epithelial surface. Mosaicism is

presented by a fine network of capillaries with honeycomb appearance, disposed parallel to the epithelial surface. Punctation and mosaicism may be seen together within the same area of the cervix. (Figure 9.2-3)

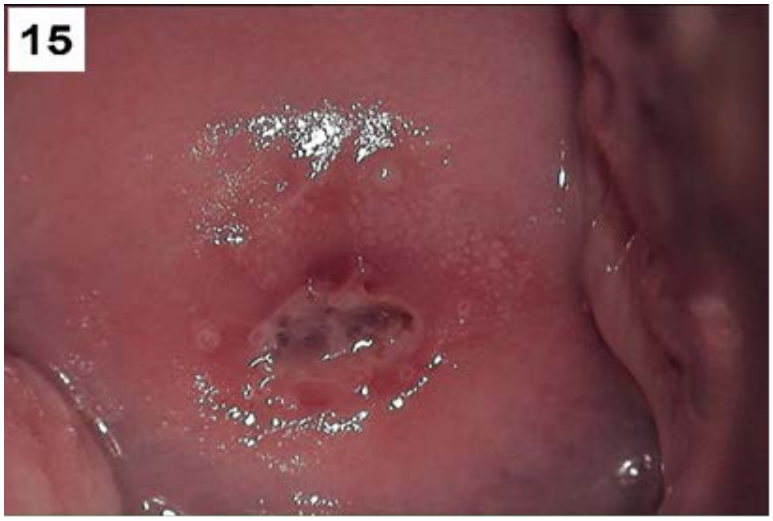


Figure 9.3-3 Changed vascular pattern. Here mosaicism

In invasive carcinoma the pattern of the terminal vessels is various. In addition to punctuation and mosaicism, corkscrew-shaped, comma-shaped, dilated blind ended vessels presented.

CIN requires cervical biopsy. In satisfactory colposcopic findings, a punch biopsy along with the endocervical curettage is performed. If there are unsatisfactory colposcopic findings and high-grade lesions in Pap smear, a diagnostic cone biopsy is indicated.

The standard algorithm for diagnosis of CIN is cervical cytology, or Pap smear, if cytology results are positive, then subsequent colposcopy; biopsy suspicious lesions with histological examination are performed. Histologically confirmed CIN requires observation, while CIN II + requires special treatment. (Table 9.2-1) The main goal of screening-

treatment programme is to reduce incidence of cervical cancer and associated with it mortality rates.

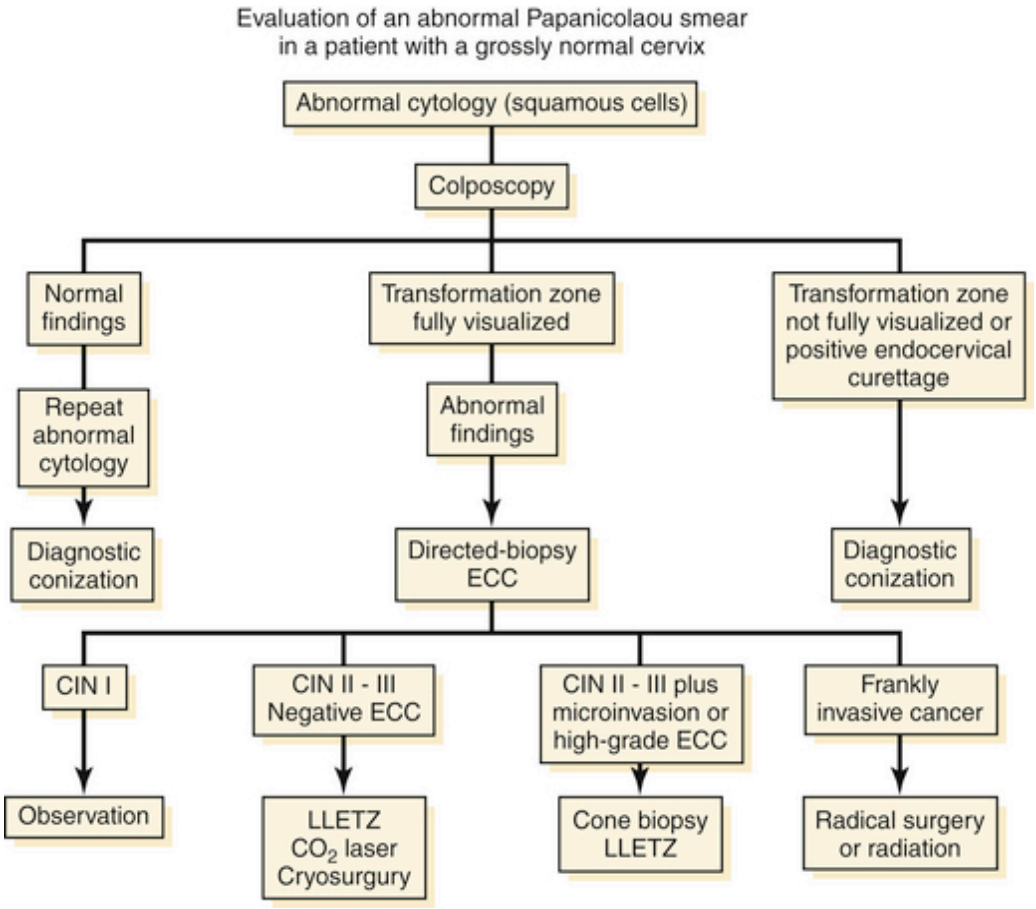


Table 9.2-1 Algorithm for evaluation of patients with an abnormal Pap-smear

Common screening tests that are widely used for diagnosis of CIN are test for HPV, Pap test and visual inspection of the cervix with administration of acetic acid.

Treatment options for cervical intraepithelial lesions are loop electrosurgical excision, cryosurgery, carbon dioxide laser and cold-knife conization, hysterectomy.

Active treatment is indicated for CIN I, II, III.

The loop electrosurgical excision is the most common method for treatment of CIN. The advantages of this method are possibility to perform on an outpatient basis under local anesthesia, to excise large specimens with a minimal amount of thermal damage, minimal risk of bleeding, it is cheap and fast procedure. Complications of LEEP (loop electrosurgical excision procedure) are bleeding, cervical stenosis, and infection. Using excessive amount of electricity may cause diathermy artifact that may result in wrong histological interpretations.

In the last 20 years using of the carbon dioxide laser for the treatment of cervical lesions became more popular. The CO2 laser produces a monochromatic beam of light in the infrared portion of the spectrum, which focused through the system of lenses and mirrors. The main action of the laser is vaporization, boiling of the intracellular water of the cervical tissue, and thus, destroying contacted pathological areas. The procedure is done under local anesthesia. CO2 laser also can be used as cutting tool. The advantages of the laser treatment are possibility to control the depth of the vaporization, low risk of bleeding, absence of postoperative scars, low rates of failure. (Figure 9.2-4) Complications are rare, generally associated with immediate and delayed bleedings and infection. As laser equipment is very expensive it is not available widespread.

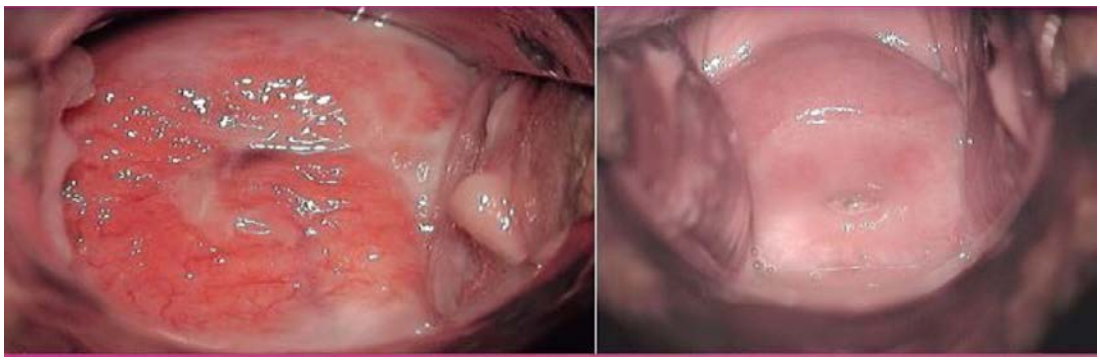


Figure 9.2-4 Cervix before and after the treatment with CO2 laser

One of the most effective therapeutic options for the treatment of cervical dysplsia is cryosurgery. The mechanism of cryosurgery is cooling of tissue until cryonecrosis has occurred. Freezing of the tissue is followed by crystallization of the intracellular fluid with subsequent rupturing of the cells and denaturation of cell proteins. Usually nitrois oxide is used. The advantages of cryosurgery are possibility to perform the procedure without anesthesia, absence of bleeding and low cost. But it has side effect and complications. These are a high failure rates for large lesions, painful cramps due to prostaglandins synthesis, and excessive watery vaginal discharge, that lasts for 2-3 weeks.

Cervical conization is the procedure that was widely used for a diagnostic purpose. It was also used for the treatment of the cervical lesions before the laser and cryotherapy were inducted to the gynecological practice. A great number of complications, such as bleeding, cervical stenosis, cervical incompetence, infection limit the wide use of cold-knife conization. The use of conization is indicated only in situations, which require large area of conization, or if

histological evaluation is critical and the risk of even a small artifact may affect the result of examination.

In case if cervical dysplasia is followed by uterine or adnexal disease hysterectomy is may be applicable.

Chapter review

1. Which types of HPV are responsible for 70% of cervical cancer?

A) 16 and 18

B) 6 and 11

C) 16 and 11

D) 16 and 35

E) 11 and 18

2. What age should annual Pas smear examination be performed since?

A) Within 3 years of sexual life or age 21

B) Within 1 year of sexual life

C) Starting from 18 year

D) Starting from 20 year

E) No matter

3. Which type of epithelial cells is endocervix covered by?

A) Single layer of columnar epithelium

B) Nonkeratinized squamous epithelium

C) Ciliar epithelium

D) Glandular epithelium

E) Simple cuboidal

4. Gardesil is the vaccine against types of HPV:

A) 6, 11, 16, 18

B) 6, 11

C) 16, 18

D) 16, 18, 30, 35

E) 6, 11, 30, 35

F) 30, 35

5. The most common diagnostic methods for cervical pathology are:

A) Cervical cytology and colposcopy

B) Cervical biopsy

C) Speculum examination of the vagina

D) Hysteroscopy

E) Cervical cytology and bimanual examination

6. Which of the following is not a risk factor for cervical cancer?

A) Infertility

B) High parity

C) Smoking

D) Multiple sexual partners

E) Early onset of sexual life

7. Which of the followings are colposcopic characteristics of the transformation zone?

A) Presence of gland openings and pale coloration of the metaplastic epithelium

B) Presence of nabothian cysts

C) Red-velvety area around the external cervical ox

D) Grape-like appearance

E) Has the same appearance as original squamous epithelium

8. What is a treatment option for CIN I?

A) Observation with repeating of smear after 6 month

B) Large loop excision

C) Carbon dioxide laser

D) Cryosurgery

E) Hysterectomy

9. The followings are disadvantages of laser therapy of cervical lesions:

A) High cost and not widespread availability

B) High incidence of bleeding and scarring

C) Lead to cervical stenosis and incompetence

D) Require regional anesthesia

E) Prolonged period of healing and high rate of treatment failure

10. Which of treatment options is used in case when large area of conization is required?

A) Cold-knife conization

B) Cryosurgery

C) Hysterectomy

D) Large loop excision

E) Laser conisation

Chapter 10 Breast Diseases

10.1 Screening of the Breast

Breast disease is one of the actual problems of modern oncogynecology.

High incidence of benign breast pathologies significantly increases the risk for breast cancer. Benign breast disorders are the most common pathological processes in women of different age groups, and the incidence increased with age from a rate of 20-25% for women ages 25-30 to 60% for women 40 years and more. The term “benign breast diseases” encompasses a heterogenous group of lesions that may present a wide range of symptoms. The most common benign disorders of the breast are fibrocystic changes.

At the present breast cancer is the most common female malignancy. More than 800000-1000000 new cases of breast cancer are diagnosed annually all over the world. This incidence is increasing annually on 3%, and is the most common mortality cause in women of age 40-44. It is more evident in well developed countries with high urbanization processes, so the incidence of breast cancer in France is 28%, in USA-29%, in Sweden-25%, in Japan-13.9%. In North America and northern Europe the incidence and mortality rates of breast cancer are 5 times higher than they are in Asia and Africa. In Azerbaijan breast cancer is also in the leading point in the structure of female oncologic diseases, with incidence 15.5%.

Results of a numerous studies show that the risk of breast cancer is significantly increasing at atypical changes of epithelium. That's why benign breast disorders have a great interest as a possible background for malignancy. The followings are the risk factors for developing breast diseases:

1. Hereditary predisposition
2. Hormonal factor
3. Reproductive factors
4. Lactation
5. Age
6. Trauma
7. Inflammatory diseases of breast
8. Dietary factors
9. Psychological factors
10. Smoking

Established risk factors for breast cancer are presented in a Table 10.1-1

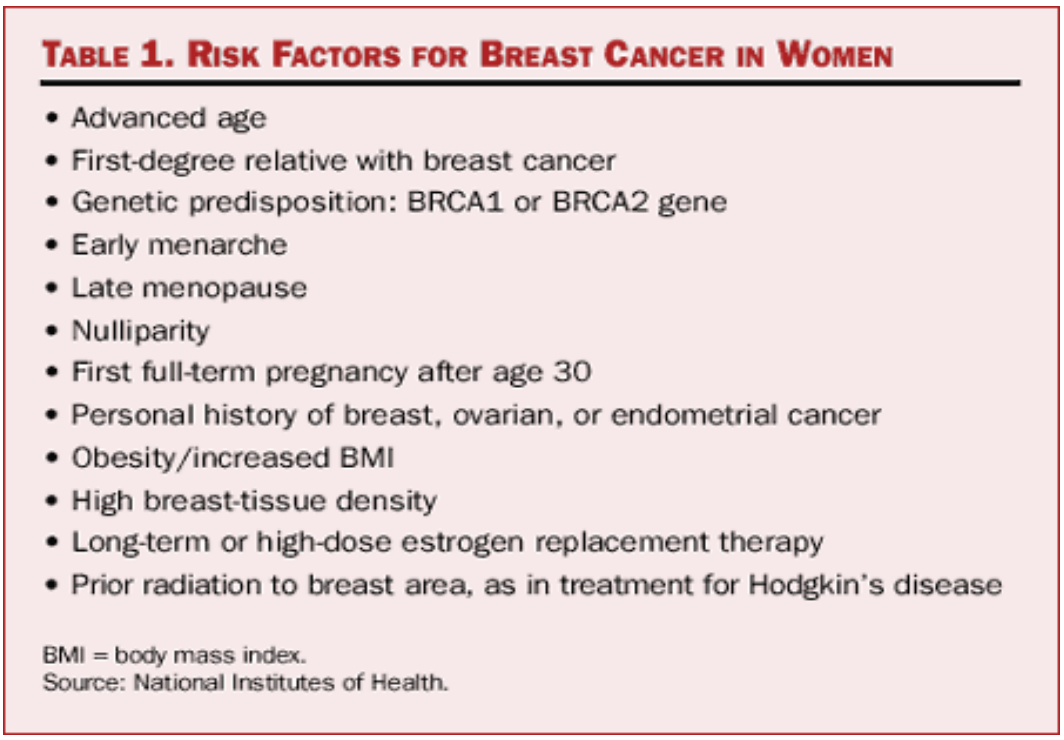


TABLE 1. RISK FACTORS FOR BREAST CANCER IN WOMEN

- Advanced age
- First-degree relative with breast cancer
- Genetic predisposition: BRCA1 or BRCA2 gene
- Early menarche
- Late menopause
- Nulliparity
- First full-term pregnancy after age 30
- Personal history of breast, ovarian, or endometrial cancer
- Obesity/increased BMI
- High breast-tissue density
- Long-term or high-dose estrogen replacement therapy
- Prior radiation to breast area, as in treatment for Hodgkin's disease

BMI = body mass index.
Source: National Institutes of Health.

Table 10.1-1 Established risk factors for breast cancer

Regular screening of the breast is very important for diagnosis and prevention of benign and malignant breast diseases. Screening is including:

-self breast examination

-breast examination by physician

-mammography

-ultrasound examination

Many women detect breast diseases by themselves during self-examination. Breast self-examination (BSE) should be done monthly. It gives possibility to be more aware of breast condition. The most

favorable time for BSE is within a week after period, when breasts are not swollen or tender. The procedure should be done in the upright position, starting from carefully inspection of the breast initially by arms on the side, then by arms raised above the head. Supraclavicular and axillar areas should be palpated for the presence of nodes. After that, women should lie down and continue palpation of all the quadrants of the breast with the flat of her fingers. The final step is palpation of the areolas and compression of the nipples for evidence of discharge. (Figure 10.1-1)

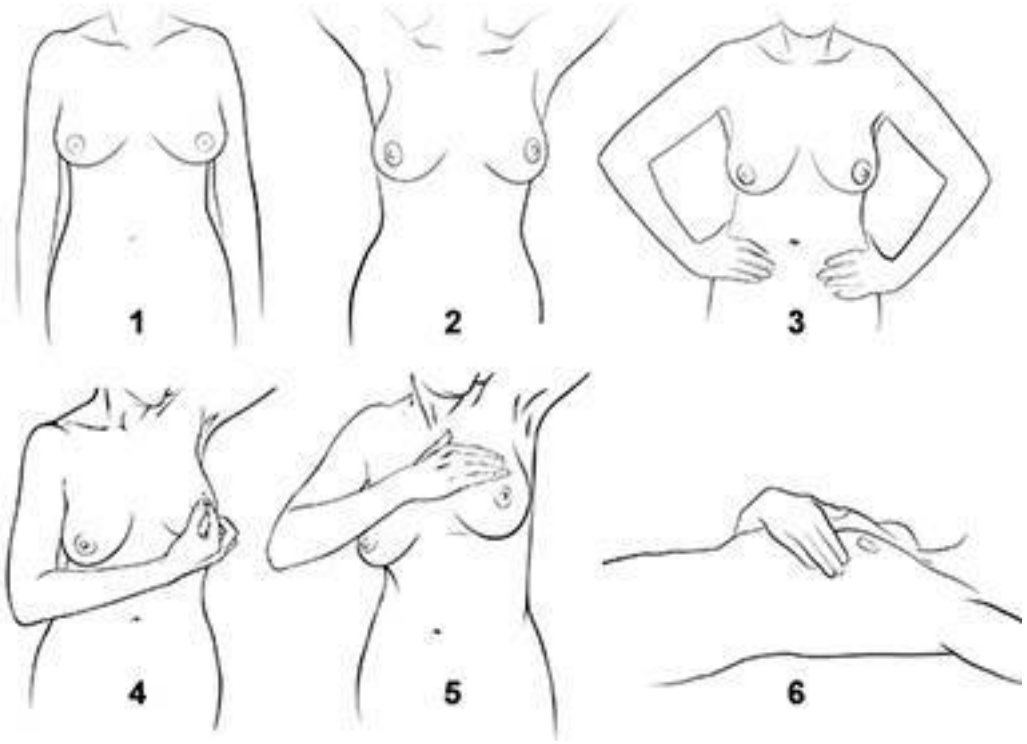


Figure 10.1-1 Illustration of self breast examination

A clinical breast examination is performed by a physician. Different types of abnormalities can be detected during examination. Initially appearance, contour and symmetry, skin changes and nipple retraction

should be checked. Examination is starting in an upright position. Patient is asked to raise her arms over her head, hang by her sides, or press her hands against hips. Skin retraction, because of malignancy, is more highlighted by having the patient extend her arms over her head. In this position axillar area should be carefully palpated. Using the pads of the fingers, physician checks entire breast, areola, nipple, underarm, and supraclavicular area for evidence of lymphadenopathy. After that the examination is repeated in the supine position. If any lump is discovered, physician should note its size, shape, and texture. Benign lesions usually appear as soft, smooth, round, and mobile formations. The hard, oddly-shaped, and firmly attached within the breast formations are more likely to be a cancer.

Mammography is a radiologic examination of the breast, and it is useful in discovering of small tumors in asymptomatic patients. Mammography is an important component of the breast screening program. The American Cancer Society recommends cancer screening guidelines for women:

-ages 40-44 should start annual mammograms if they wish

-ages 45-54 should get annual mammograms

-age 55 and older should switch to mammograms every 2 years, or can continue yearly screening

-screening should be continue as long as woman is in good health and is expected to live 10 more years or longer

Mammography helps to find cancer in about 8 of every 1000 women having screening. (Figure 10.1-2)

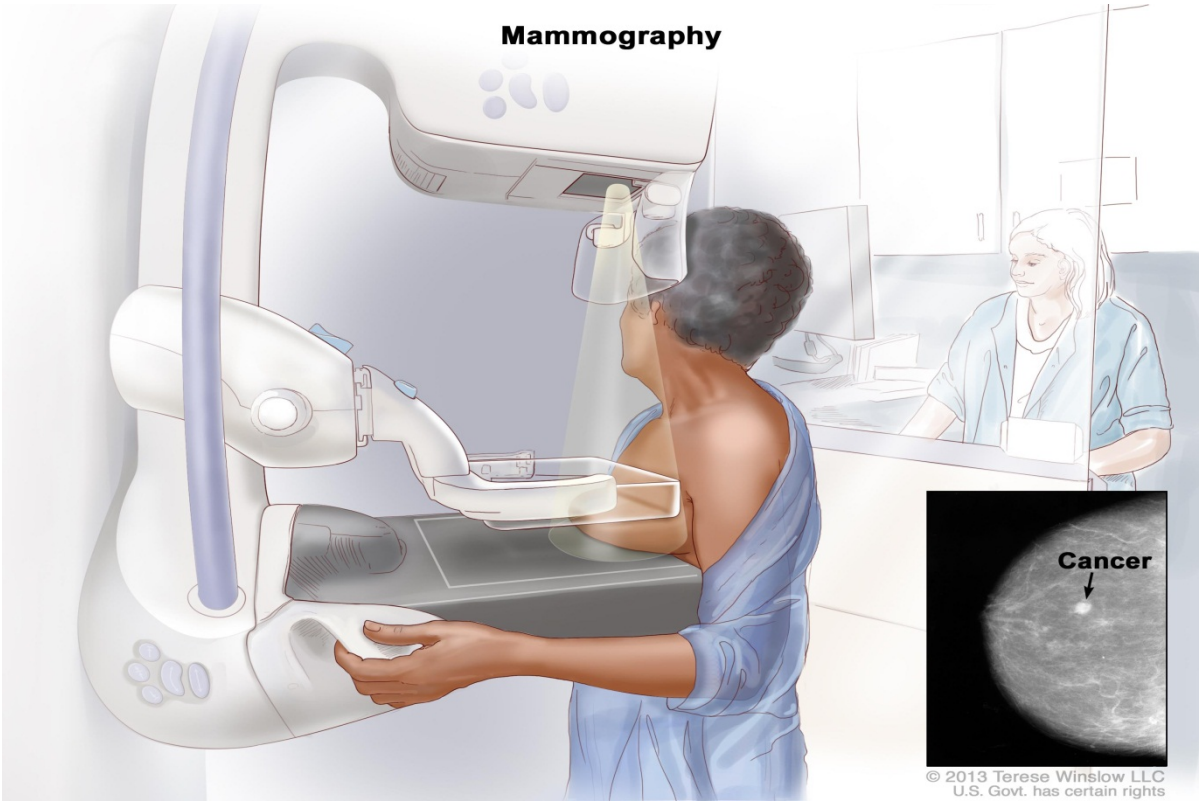


Figure 10.1-2 Procedure of mammography

Breast screening takes 2 x-rays of each breast, one from above, and one from the side. Mammograms can be made with about 0.3 cGy or less radiation, so there is a little risk for this technique causing breast cancer. But statistics show that 3-6 cases of breast cancer among 10000 examined women, which have regular 3 year screening, are caused by radiation.

Breast cancers found by screening are generally at an early stage. Women who are diagnosed with breast cancer at the earliest stages have a 9 in 10 chance of surviving for at least 5 years after diagnosis.

Ultrasound examination is beneficial in differentiation of solid forms of tumors from the cystic forms. Usually it is performed in addition to a mammography, or in women younger than 35 years, when mammography is not informative due to young women have denser breasts, which often look white on mammograms. For these women, a breast MRI is likely to be more accurate and safer procedure.

If suspicious changes are found, for distinguishing if they are malignant or benign, fine-needle biopsy or open biopsy is indicated. Fine-needle biopsy with subsequent cytologic evaluation is outpatient procedure. It is both specific and sensitive, and allows make definitive diagnosis of breast cancer in 90% of cases without open biopsy. It the cystic mass contains bloody fluid and doesn’t collapse after needle aspiration, or spontaneous serous or serosanguineous nipple discharge in the absence of a mass occurs, then open breast biopsy is indicated. Open breast biopsy may be performed under local or general anesthesia.

Regular breast screening, avoiding of risk factors, such as long lasting hormonal therapy, obesity, smoking, and improving of lifestyle are the main goals of preventing breast diseases.

10.2 Benign Breast Disorders

Benign breast disorders (BBD) include a range of clinical and pathological non malignant breast conditions. A pathologically heterogenous group of benign breast lesions were recently termed as

fibrocystic disease or fibrocystic changes. At present all benign breast disorders are divided into three categories:

-non proliferative lesions of the breast

-proliferative breast disorders without atypia

-atypical proliferative lesions

BBD can be classified into following groups:

1. Aberrations of normal development and involution
2. Pathological classification
3. Clinical classification
4. Classification based on the risk for malignancy

The most common benign non-proliferative lesion of the breast is fibroadenoma. Fibroadenoma is composed of both fibrous and epithelial elements. They can occur in any age, but generally in women before 30 years. Fibroadenomas are well circumscribed firm spherical lesions surrounded from the normal breast tissue by kind of pseudocapsula. The diameter of fibroadenoma may vary from 2-4 cm to 15 cm more characteristic to giant forms, which prone to malignancy. They are stimulated by estrogens, so may increase during pregnancy and undergo regression in postmenopause. Other less common non-proliferative lesions of the breast are adenoma, hamartoma, and adenolipoma. (Figure 10.2-1)

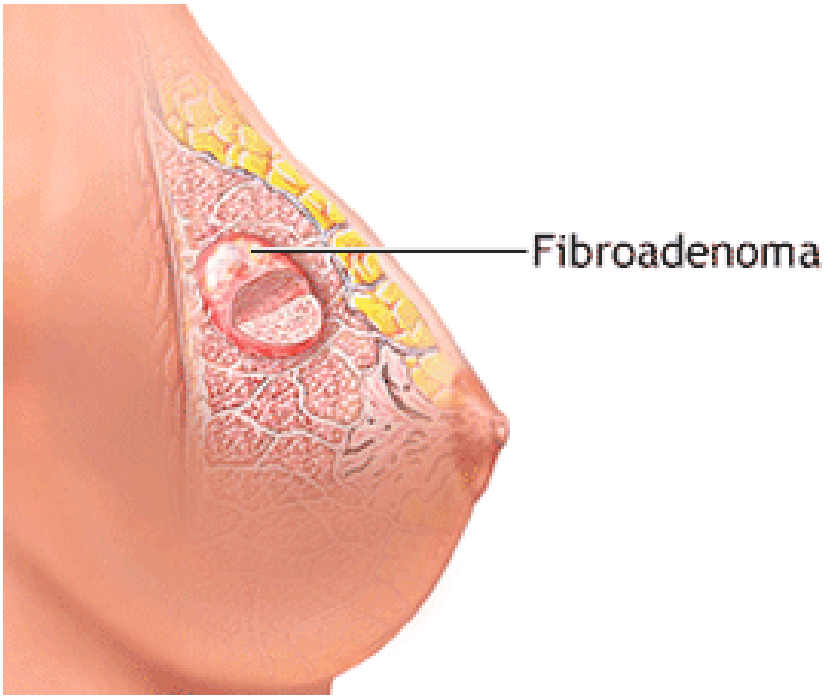


Figure 10.2-1 Breast fibroadenoma

Proliferative breast disorders without atypia include sclerosing adenosis, intraductal papillomas, fluorid epithelial hyperplasia. Sclerosing adenosis clinically resembles to cancer, and characterizes by proliferation of stroma and glandular elements. Intraductal papilloma characterizes by proliferative growth within the ducts of the breast. They may be solitary or multiple, have pink or nude coloration and attached to the wall of the duct by a stalk. They are not palpable, and usually are displayed by bloody, serous, or turbid discharge from the nipple. Solitary lesions are most common in premenopausal women, and rarely undergo malignant transformation. Multiple intraductal papillomas are more evident in younger patients, and more likely undergo malignant transformation. Mammography and cytologic examination of the nipple discharge are helpful in differential diagnosis. (Figure 10.2-2)

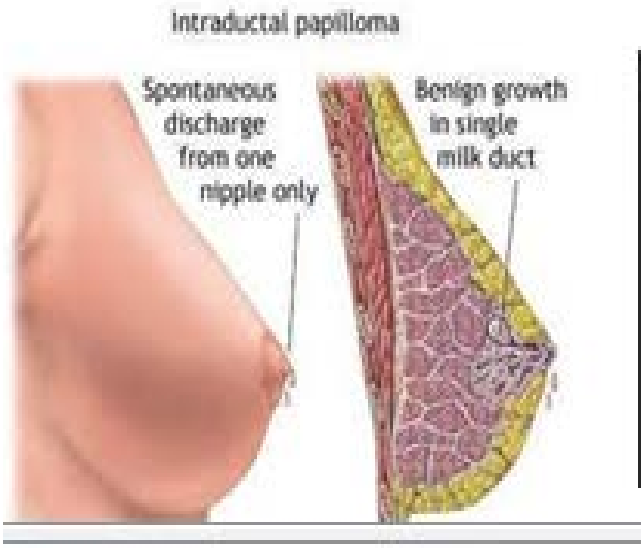


Figure 10.2-2 Breast intraductal papilloma

The most common proliferative benign disorder of the breast is hyperplasia. The incidence of breast hyperplasia is very high, and is presented in about 50% of women. It can be lobular or ductal. If hyperplasia is associated with cellular atypia, the risk of malignant transformation is significant. The main etiologic cause of breast hyperplasia is hormonal imbalance. Absolute decrease in progesterone synthesis and increase in estrogen level stimulate hyperplastic processes in breast tissues. Estrogen stimulates the proliferation of mammary ducts and stroma, whereas progesterone is responsible for proliferation of lobular and alveolar structures. These lesions significantly regress during pregnancy due to elevated progesterone producing. Lesions are usually multiple and bilateral. Hyperplasia may occur at any age, but most common in premenopausal women. In patients of reproductive age hyperplasia is characterized by premenstrually pain and tenderness of the breast.

There are also a variety of inflammatory and reactive lesions of breast. The most common of them are mastitis, foreign body reactions, and recurrent subareolar abscess.

Benign breast disorders are characterized by the following clinical symptoms:

-physiologic tenderness and swelling, related with a menstrual cycle

-nodularity, which can be granular or grossy, sometimes involving entire breast

-mastalgia, may be cyclic or non cyclic.

-dominant masses and discreet lumps

-nipple discharge, may be bloody, serous, or galactorrhoea (discharge of milk like fluid secondary to the breast stimulation by elevated prolactin secretion)

-symptoms of inflammation: pain, edema, erythema, tenderness, local rise of temperature

Diagnosis of BBD is based on clinical and radiologic findings. Mammography, ultrasound examination and MRI are used for diagnosis of breast lesions. Some large lesions require surgical excision for definitive diagnosis. (Figure 10.2-3)

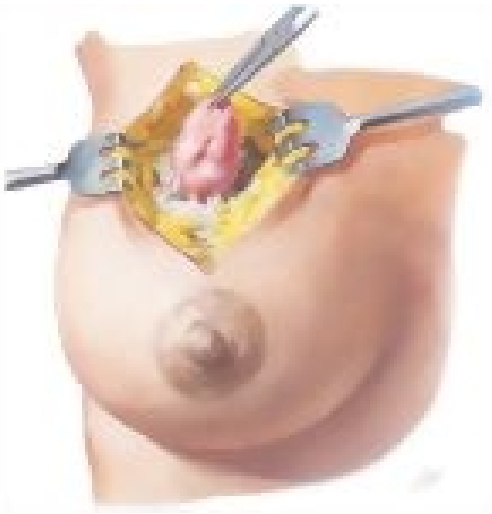


Figure 10.2-3 Diagnostic excision of the breast

Treatment of BBD depends on the results of diagnostic procedures. Most of BBD can be managed non-surgically. Conservative treatment includes endocrine, nonendocrine, and nutritional therapies. Such pathologies, as intraductal papilloma and fibroadenoma require surgical excision for both diagnosis and treatment. If there are small palpable cysts, fine-needle biopsy with aspiration of the fluid till dryness is a treatment of choice. Atypical transformations require specific treatment.

Chapter review

1. What is the incidence of benign breast disorders among women of 40 yars and older?

A) 60%

B) 40%

C) 20-30%

D) 15%

E) 40-50%

2. Which of the following is not a risk factor for breast cancer?

A) Multiparity

B) Obesity

C) Hormonal imbalance

D) Hereditary factor

E) Smoking

3. The screening of the breast includes all of the below except :

A) CT of the breast

B) Breast self-examination

C) Breast examination by physician

D) Ultrasound examination

E) Mammography

4. The recommended age for the onset of annually mammography is:

A) 40-44 years

B) 30-35 years

C) 25-30 years

D) 30 years

E) 50 years

5. Which diagnostic procedure is performed in case if the cystic lesion contains hemorrhagic fluid and doesn’t collapse after fine-needle aspiration?

A) Open breast biopsy
B) Large breast excision
C) Ductography
D) Mammography
E) Fine-needle biopsy

6. Which of the following is not a cause of a pathologic nipple discharge in the non-lactating breast?
A) Microadenoma of the pituitary gland
B) Intraductal papilloma
C) Carcinoma
D) Fibrocystic changes
E) Duct ectasia

7. The intraductal papilloma is most common in:
A) Premenopausal women
B) In women of reproductive age
C) In patients with hormonal imbalance
D) In women of age 60-70 years
E) In nulliparous women

8. What is the most common proliferative benign disorder of the breast?
A) Hyperplasia
B) Fibroadenoma
C) Intraductal papilloma
D) Mastitis
E) Galactorhea

9. What is the workup of a 25-year-old with a palpable breast mass?

A) Breast examination by physician, ultrasound, fine-needle biopsy with cytologic examination

B) Breast-self examination, ultrasound, open biopsy

C) Mammography, fine-needle biopsy

D) Breast examination by physician, mammography, fine-needle biopsy

E) Breast examination by physician, mammography, open biopsy

10. Ductal proliferation is depend on what hormone?

A) Estrogen

B) Prolactin

C) FSH

D) Testosterone

E) Progesterone

Chapter 11 Ectopic Pregnancy

An ectopic pregnancy defines as a pregnancy in which fertilized egg implants and develops outside the uterine cavity. Despite possibility of early diagnosis, it continues to represent a serious hazard to maternal life and future reproductive potential. It is one of the leading causes of early pregnancy hemorrhages, and the most common cause of pregnancy-related death in the first trimester (3-6%). The incidence of ectopic

pregnancy is 1-6% of all gynecological pathology. It is estimated that 1 of every 80 spontaneous pregnancies is ectopic. It is usually occurs in women of age 20-35 years, generally in multigravid women. Incidence of ectopic pregnancy in nulligravid women is 10-15%.

The incidence of ectopic pregnancy has tendency to rising due to increased number of inflammatory processes of reproductive organs, especially related to Chlamydia trachomatis, surgical intervention on fallopian tubes, and using of in vitro fertilization and other assisted reproductive technologies. (Figure 11-1)

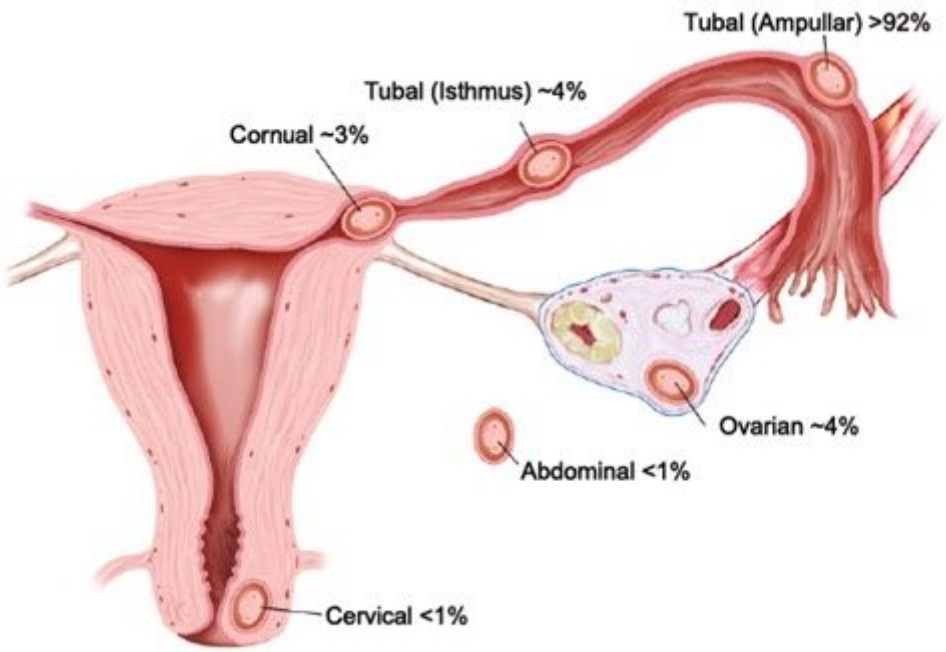


Figure 11-1 Common cites of ectopic pregnancy

The etiology of ectopic pregnancy is not always clear, but it is associated with a range of factors that predisposing to abnormal

transport and implantation of the fertilized egg. The followings are the risk factors for ectopic pregnancy:

-history of inflammatory processes of the upper genitalia

-prior ectopic pregnancy

-history of tubal surgery

-infertility

-hormonal therapy with estrogens and progestines, stimulation of ovulation

-using of intrauterine device

-congenital abnormalities of reproductive organs

-endometriosis

-using of assisted reproductive technologies

-smoking

All these processes may follow by the functional or anatomical alterations of the fallopian tubes, because of damage of the ciliated surface of the tubal cavity, or slowed tubal transport.

More than 95% of ectopic pregnancies are tubal. Other, less common sites of ectopic pregnancy are ovary, cervix, rudimentary uterine horn, abdominal cavity. These organs doesn’t have proliferated mucous layer for adequate implantation of the fertilized egg. As tubal mucosa is very thin, trofoblast easily destroys it and invades into the tubal wall. Tubal vessels due to trofoblast eroding are enlarged and engorged. The

affected segment of the tube distends as pregnancy progresses. It is may follow by the vaginal bloody spotting or bleeding because of bleeding from the tube and shedding of the endometrial lining of the uterine cavity.

Tubal pregnancy may results in tubal rupture, pregnancy resorption due to restricted blood supply, and tubal abortion. If pregnancy develops in the isthmic part of the fallopian tube, rapid invading of the chorion into the tubal wall leads to it rupture at 4-6 weeks of gestation, and follows by excessive abdominal bleeding.

If the implantation of the ectopic pregnancy occurs in the interstitial segment of the tube, pregnancy may progress till 10-12 weeks.

The ampullary implantation is the most common. Incidence of the ampullary ectopic pregnancy is approximately 70-80%. Pregnancy may grow into the tubal cavity, following by tubal rupture or hematosalpings, or grows into the abdominal cavity resulting in tubal abortion with abdominal hemorrhage, or implantation of the egg in the abdominal cavity with it further development.

Sometimes ectopic pregnancy may implant over the ovary. This type of ectopic pregnancy results in rapid rupture of the implantation site and follows by the excessive bleeding.

An ectopic pregnancy classifies on:

A. Abdominal pregnancy

B. Tubal pregnancy

1. Progressing tubal pregnancy

2. Tubal rupture

3. Tubal abortion

C. Ovarian pregnancy

D. Other types of ectopic pregnancy

1. Cervical

2. in the rudimentary corn of the uterus

3. Intraligamentous

4. Combined

By clinical duration ectopic pregnancy is distinguished on progressing and interrupted.

Clinical manifestation of the ectopic pregnancy presented by characteristic triad of symptoms: lower abdominal pain, vaginal bleeding, and absence of menses. About 50% of patients have all three of these symptoms.

Abdominal pain usually starts 6-8 weeks after a missed period. As an ectopic pregnancy progresses, abdominal pain may get worse. Rupture of the implantation site may follow by sharp pain in the on one side with further spreading throughout the pelvic region. The patient may also complain on ipsilateral shoulder pain, caused by irritation of the phrenic nerve by the blood under the diaphragm. Signs of internal hemorrhage may be presented: hypotension, tachycardia, dizziness, diaphoresis, fainting, even hypovolemic shock. The abdominal wall is tender and sharply painful at palpation.

Vaginal examination may reveal slightly enlarged tender cervix and bulging of posterior vaginal fornix due to collection of the blood in the cul-de-sac. At bimanual examination uterus is enlarged and tender at palpation. However, there may not be a palpable adnexal mass.

Amenorrhea or a history of delayed recent menses is evident in 80-90% of ectopic pregnancies. Half of patients have abnormal vaginal bleeding. The degree of the vaginal bleeding varies, and may be presented by bloody spotting or excessive vaginal bleeding. The main cause of the vaginal bleeding is insufficient amount of hormones that cannot support the endometrial lining, which loses the connection with the underlying decidua basalis and shed out. The rupture of the interstitial part of the tube also may follow by the excessive vaginal bleeding.

Clinical symptoms of the ectopic pregnancy may range from mild in early stages to severe in a case or rupturing.

Tubal abortion characterizes by slowly progression of the clinical symptoms. Usually unilateral cramp-like pain in the lower abdomen, secondary to the absence of the periods, follows by abdominal bleeding with formation of the hematoma. Characteristic dark bloody vaginal discharge appears on day 2-3 of the onset of the clinical symptoms. Unlike the tubal rupture, symptoms of inner bleeding and peritoneal irritation are mild, or may be absent during the period of time.

Clinical symptoms of ectopic pregnancy are similar to those in threatened abortion, that’s why distinguishing of it may be

challenging. Also differential diagnosis for ectopic pregnancy is done with acute pelvic inflammatory disease, adnexal torsion, ruptured corpus luteum cyst, degenerating leiomyoma, acute appendicitis.

Transvaginal ultrasonography with hCG testing are helpful in diagnosis of an ectopic pregnancy. Serum levels of hCG increases in maternal blood serum with the implantation. Generally, in normal intrauterine pregnancy level of hCG is doubling every 48 hours during first weeks of gestation, so the hCG level should increase by 66%. The slow rise of hCG in the blood serum is characteristic for an ectopic pregnancy and abnormal intrauterine pregnancy. This may be suspected if the hCG levels rise by less than 53%. Repeat 48 hour serum hCG should be obtained.

Transvaginal ultrasound also has a diagnostic value. The failure to visualize an intrauterine gestational sac on transvaginal ultrasound with an hCG <2000.0 mIU/mL has a positive predictive value of 86% and specificity of 935 for ectopic pregnancy. (Figure 11-2)

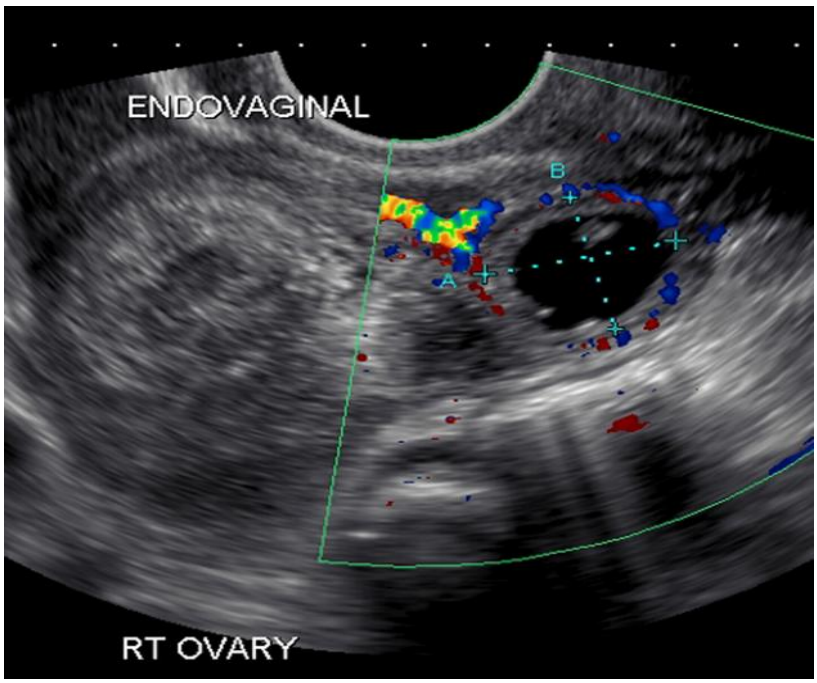


Figure 11-2 Ultrasound imaging of tubal pregnancy

Ultrasonographic findings as abnormal complex adnexal mass and adnexal gestational sac with or without an embryo are helpful in diagnosis of an ectopic pregnancy as well. A false-negative diagnosis can result from a thick decidual reaction, which can appear as an intrauterine pregnancy. The diagnosis of ectopic pregnancy may be confirmed by the absence of ultrasound visualization of an embryo in a woman with a level of hCG that is appropriate for the normal echographic image of a normal intrauterine pregnancy. (Table 11-1)

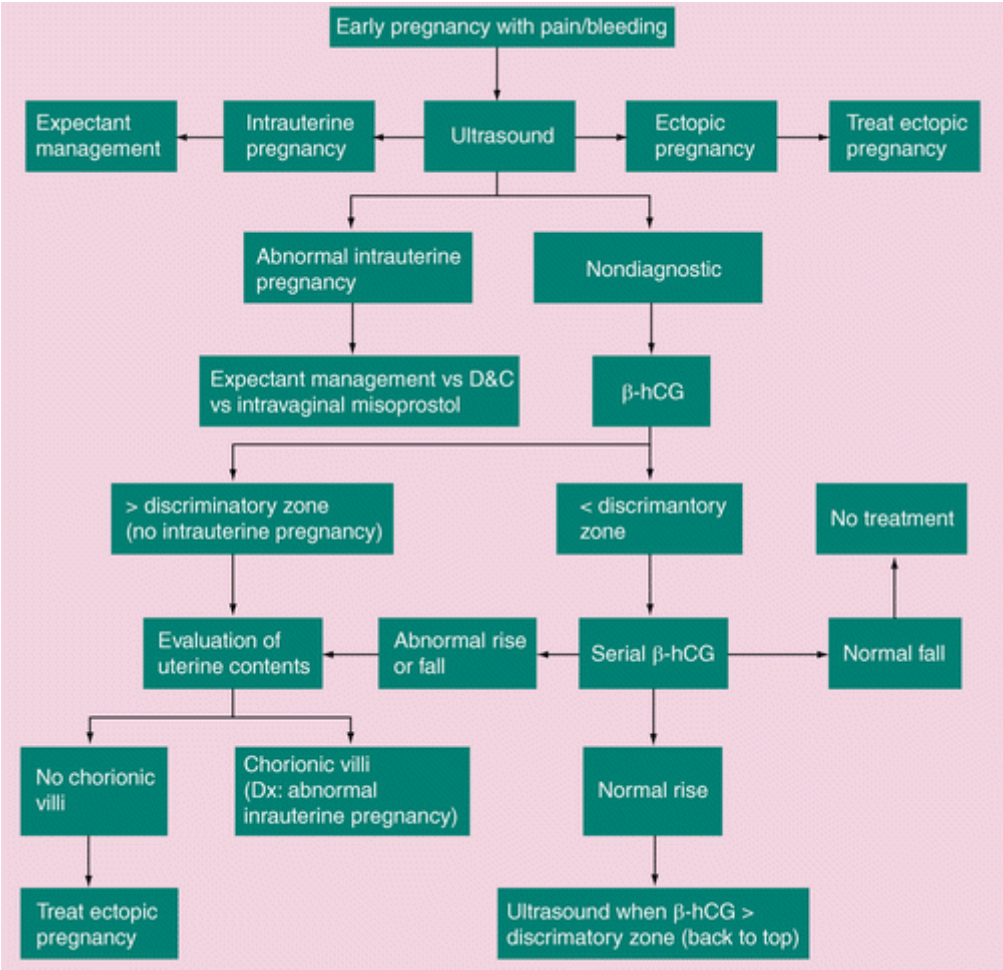


Table 11-1 Algorithm ov evaluation of patients with ectopic pregnancy

Serum progesterone levels greater than 25 ng/ml is an indication of normal pregnancy. Levels less than 5ng/ml are associated with an abnormal pregnancy. But the diagnostic value of progesterone test in a diagnosis of an ectopic pregnancy is limited.

The treatment of ectopic pregnancy is medical and surgical. Medical treatment with methotrexate is a treatment of a choice in case of early diagnosis of ectopic pregnancy without signs of rupturing in hemodynamically stable patients without active bleeding. Methotrexate is a folic acid antagonist that inhibits DNA synthesis and cell reproduction. After hCG serum level determination divided dose of methotrexate, in amount of 50 mg/m2 into each buttock is administered intramuscularly. Repeat checking of hCG levels is done on days 4 and 7 after the injection. There should be at least 15% decrease in the weekly interval hCG level with further 15% decrease every 7 days. If there is no decline in hCG levels, then the injection of the methotrexate should be repeated. In case if there is an elevation in hCG levels and clinical manifestation of the disease, surgical intervention is required.

Surgical management of ectopic pregnancy is indicated in patient with clinical signs of the rupturing and bleeding. Laparotomy is appropriate in patients, which are hemodynamically unstable and require urgent access to the bleeding site. Laparoscopy is the most preferred method of surgical treatment for ectopic pregnancy, because of short operation time and hospitalization period, less intraoperative blood loss, lower analgesic requirements, fewer incidences of

postoperative adhesions, quick recovery of the patients, and less postoperative pain.

Surgical options on the fallopian tubes include salpingectomy, salpingotomy, and salpingostomy. Salpingectomy is indicated in the following situations:

-rupturing of the ectopic pregnancy with significant damaging of the tube

-future fertility is not desired

-sterilization is required

-hemorrhage continues after salpingotomy

Partial salpingectomy is indicated if developing of the embryo is in the mid-ampullary point, and none of the indications for salpingectomy is present.

Salpingostomy is the procedure of choice for unrupted ectopic pregnancies in the ampullary portion of the tube. After identification of the implantation site, an injection of the vasoconstrictive agents is done prior to the incision. After that removal of the embryo is done with subsequent closure of the incision- salpingotomy, or left it open- salpingostomy. An incision is made parallel to the axis of the tube along its antimesenteric border over the site of implantation. Several studies have not found any significant advantages of salpingotomy over salpingostomy, but some studies show better long-term tubal function outcomes after salpingostomy. (Figure 11-3)

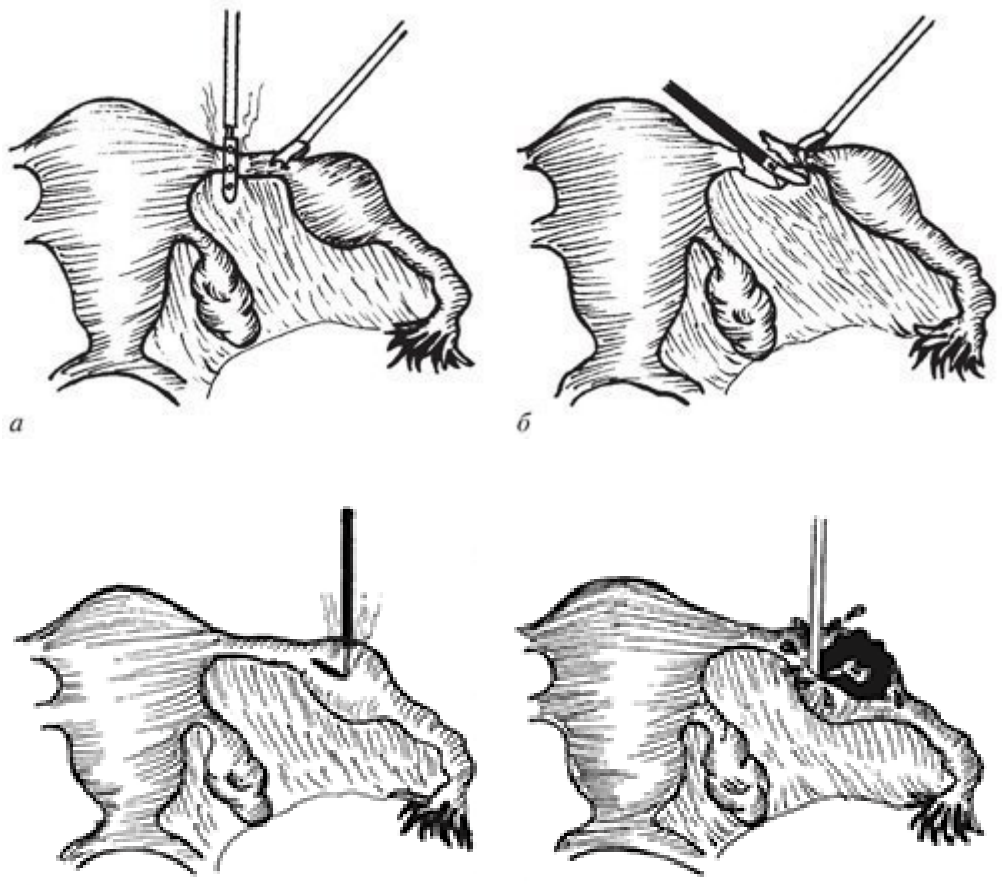


Figure 11-2 Types of laparoscopic management of tubal pregnancy: a, b) salpingectomy with cautery scisors; c) linear salpingostomy for an ampullary ectopic pregnancy

Proper pain control and hemodynamic stability are important postoperative considerations. Weekly monitoring of hCG level should be done in patients with surgical excision of the ectopic pregnancy, especially after salpingostomy. There is 5-15% risk for residual trophoblastic tissue. If there is less than 20% fall in hCG levels every 72 hours, treatment is considered incomplete, and therapy with methotrexate can be started.

Patients should be effective contraception initiated for at least three months until their hCG levels have returned to nonpregnant levels.

Chapter review

1. What percentage of gynecologic pathology ectopic pregnancy is?

A) 3-6%

B) 1-2%

C) 5%

D) 10%

E) 10-15%

2. What is the most common cause of death in women with ectopic pregnancies?

A) Acute blood loss

B) Septic shock

C) Coagulopathy

D) Embolia

E) Uterine rupture

3. Which of the following is not risk factor for ectopic pregnancy?

A) Prior cesarean delivery

B) Pelvic inflammatory disease

C) Assisted reproductive technology use

D) History of tubal surgery

E) Endometriosis

4. What is the most likely site of an ectopic pregnancy within the tube?

A) Ampullary portion

B) Interstitial portion

C) Uterine angle

D) Mid-portion

E) Fymbria

5. What is the source of an abdominal pregnancy?

A) Tubal abortion

B) Fertilization in the pelvic cavity

C) Migration of the zygote to the abdominal cavity

D) Implantation of the embryo outside the uterine cavity

E) Tubal rupture

6. Which clinical symptoms are characteristic for an ectopic pregnancy?

A) Lower abdominal pain, delayed menses, vaginal bleeding

B) Dull abdominal pain and vaginal bleeding

C) Amenorrhea and lower abdominal pain

D) Excessive vaginal bleeding, acute abdominal pain

E) Ipsilateral shoulder pain, amenorrhea, excessive vaginal bleeding

7. What is the percentage of the delayed menses in patients with ectopic pregnancy?

A) 80-90%

B) 100%

C) 60-80%

D) 50%

E) 70-80%

8. What progesterone level predicts a normal intrauterine pregnancy?

A) Greater than 25 ng/ml

B) Less than 25 ng/ml

C) 20 ng/m

D) 10-15 ng/mL

E) Greater than 40 ng/mL

9. Name the series of tests are considered to have the most diagnostic value of early ectopic pregnancies

A) Serial hCG level determination and transvaginal ultrasound

B) Serial hCG and hysteroscopy

C) Sunction of the posterior vaginal fornix and transvaginal ultrasound

D) Serum hCG level and CT

E) Urine hCG level and transvaginal ultrasound

10. When should salpingectomy not be performed?

A) Progressing ectopic pregnancy in the ampullary site

B) Devere damage of the tube

C) Desire of the patient for sterility

D) Recurrent ectopic pregnancy in the same tube

E) Ectopic pregnancy in the interstitial portion of the tube

Chapter 12 Pelvic Organ Prolapse

The term genital prolapse refers to protrusion of the pelvic organs into the vagina or beyond the vaginal opening as a result of a weakness of the endopelvic fascia, muscles of the pelvic floor and ligamentous supports. Pelvic organ prolapse and urinary incontinence are common conditions affecting pre- and postmenopausal women. (Figure 12-1)

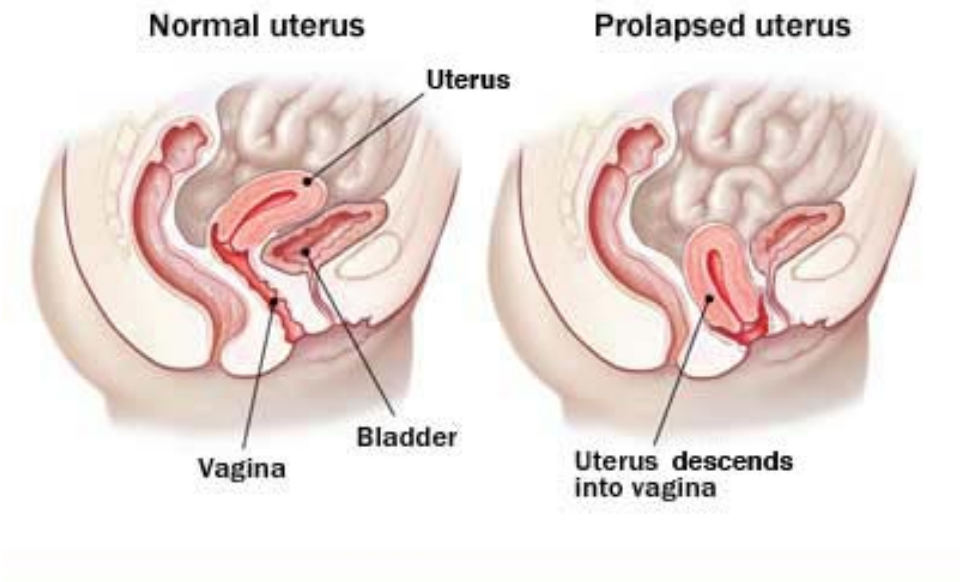


Figure 12-1 Illustration of a normal and prolapsed uterus

The incidence of POP is difficult to determine, but it is more prevalent in developed countries. Asian and black women are less likely than the white women to develop prolapse. In the Woman's Health Initiative study was found out that a 41.1 % prevalence of POP at a standard physical assessment in postmenopausal women older than 60 years who had not had hysterectomy. A woman's lifetime risk of surgery for pelvic organ prolapse is 11-19%.

Older terms describing POP, such as cystocele, rectocele, enterocele have been replaced by more anatomically precise terms, as anterior , lower posterior, upper posterior, and apical vaginal prolapse. The most common type of POP is anterior vaginal prolapse.

The pelvic organs are supported within the pelvis by levator ani muscles and the endopelvic fascia. Levator ani muscles are connected medially by the levator hiatus. The urogenital diaphragm covers the levator hiatus inferiorly. Superiorly it covered by the endopelvic fascia, which invests the pelvic organs and forms supporting ligaments. Genital prolapse occurs when this support structure is weakened through direct muscle trauma, neuropathic injury, and disruption or stretching.

The followings are the risk factors for POP:

-ethnicity

-advanced age

-obesity

-vaginal delivery

-increased intraabdominal pressure

-multiparity

-macrosomic fetus

-previous hysterectomy

-history of forceps and vacuum extractor administration

Pregnancy itself, without vaginal birth has been a risk factor as well. But multiparous women are at greater risk for POP. Excessive stretching may occur as a result of pregnancy, labor, and vaginal birth with forceps and vacuum extraction assistance.

Genital atrophy and hypoestrogenism in menopausal women are main contributors of prolapse pathogenesis. Prolapse may also result from pelvic tumors, sacral nerve disorders, and diabetic neuropathy. Increased intraabdominal pressure resulting from a chronic cough, ascites, lifting of excessive weights, constipation is predisposing factor for POP as well. Estrogen deficiency in menopausal women is one of the risk factors for urinary incontinence, involuntary loss of urine. The incidence of urinary incontinence is 15-50% in whole women population, mainly in menopausal women. The main risk factors for urinary incontinence in women are pregnancy, childbirth, menopause, hysterectomy, obesity, smoking, central nervous system problems, constipation, and urinary tract infections. The most common type of urine incontinence is stress urinary incontinence.

There are a number of classifications or grading systems for POP, but the most practical is The Pelvic Organ Prolapse Quantification system (POPQ) devised by the International Continence Society. It is based on the position of the most distal portion of the prolapse during straining (Figure 12-2):

>Stage 0: no prolapse

>Stage 1: more than 1 cm above the hymen

>Stage 2: within 1 cm proximal or distal to the plane of the hymen

>Stage 3: more than 1 cm below the plane of the hymen but protrudes no further than 2 cm less than the total length of the vagina

>Stage 4: there is complete eversion of the vagina

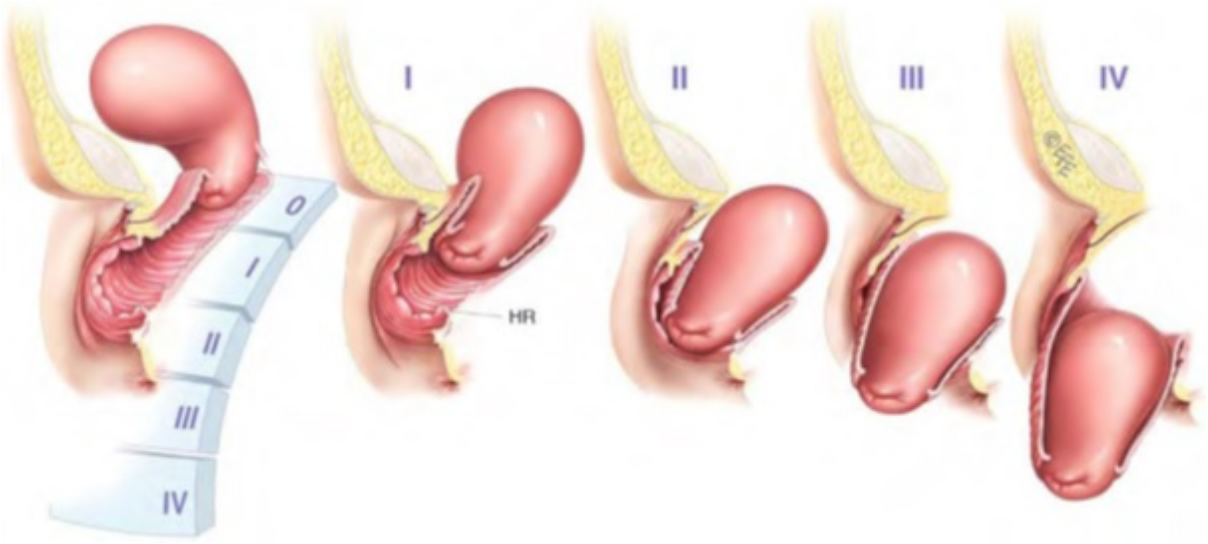


Figure 12-2 Staging of uterine prolapse

The degree of the uterine descent can also be graded by the Baden-Walker or Beecham classification systems:

>1st degree: cervix visible when the perineum is depressed-prolapse is contained within the vagina

>2nd degree: cervix prolapsed through the introitus with the fundus remaining in the pelvis.

>3rd degree: complete prolapse- entire uterus is outside the vaginal opening.

Vaginal examination in a supine position with using of single-blade speculum during relaxation, and during maximal straining is performed. First speculum is placed into the posterior vagina, allowing visualization of the anterior wall. While depressing the posterior vaginal wall, the patient is asked to strain down. The points of maximal descend of the anterior, lateral, and apical walls and their relation to the ischial spines and hymen are noted. Similarly, retraction of the anterior vaginal wall during straining allows evaluate posterior vaginal wall and determine presence of rectocele or enterocele. Next step is evaluation of the lateral vaginal support system by placing 2 fingers into the vagina such as each finger opposes the ipsilateral vaginal wall. Repeat the examination in standing position and bearing down helps to note the maximum descent of the uterine prolapse. For distinguishing of rectocele from an enterocele, rectal-vaginal examination is indicated.

Although many women with POP do not demonstrate any symptoms, the followings are the most common symptoms of prolapse:

-a feeling of pelvic pressure

-a feeling of something is falling out of the vagina

-low back pain

-dyspareunia

-spotting or bleeding from the vagina

-urinary incontinence or frequent urination, especially at night

Women with anterior vaginal prolapse complain on feeling of vaginal fullness, heaviness, pressure, and discomfort that are most noticeable after prolonged standing or straining. Also they have problems with urination such as urine incontinence, frequent urination, and nocturia. Women may have to press the anterior vaginal wall to empty their bladder completely. Women with 3rd or 4th stage of prolapse may demonstrate urethral obstruction.

Patients with posterior vaginal wall prolapse along with the common symptoms as feel of heaviness, fullness of the vagina, discomfort, have problems with bowel dysfunction and defecation. Upper posterior vaginal wall prolapse is associated with Duglas pouch herniation resulting in enterocele.

The failure of all the vaginal supports results in complete uterine prolapse, or complete procidentia. Vaginal vault prolapse occurs after vaginal or abdominal hysterectomy and represents failure of the supports around the upper vagina. Patients with complete procidentia may have ulceration of the prolapsed area, bleeding, purulent discharge, and rarely cervical carcinoma. This condition affects the quality of life and cause serious psychological problems.

Asymptomatic patients do not require any therapy. However, when the symptoms occur, patients with mild uterine prolapse may need conservative treatment. When there is a mild degree of pelvic relaxation, pelvic floor exercises may improve the tone of the pelvic floor musculature. Kegel’s exercises performed routinely can improve pelvic floor muscle tone and stress urine incontinence. Topical

estrogen therapy and intravaginal administration of pessaries for support are the mainstays of nonsurgical management of patients with POP. Pessaries may be used to correct prolapse by ‘propping up” the vagina. Many different types of the pessaries exist. (Figure 12-3) Pessaries can be considered when the patient is medically unfit or refuses surgery, or during pregnancy and postpartum period. Pelvic inflammatory disease and personal intolerance are contraindications for pessaries administration. They can cause irritation and ulceration of the vagina, and should be removed and cleaned every 6 to 12 weeks.

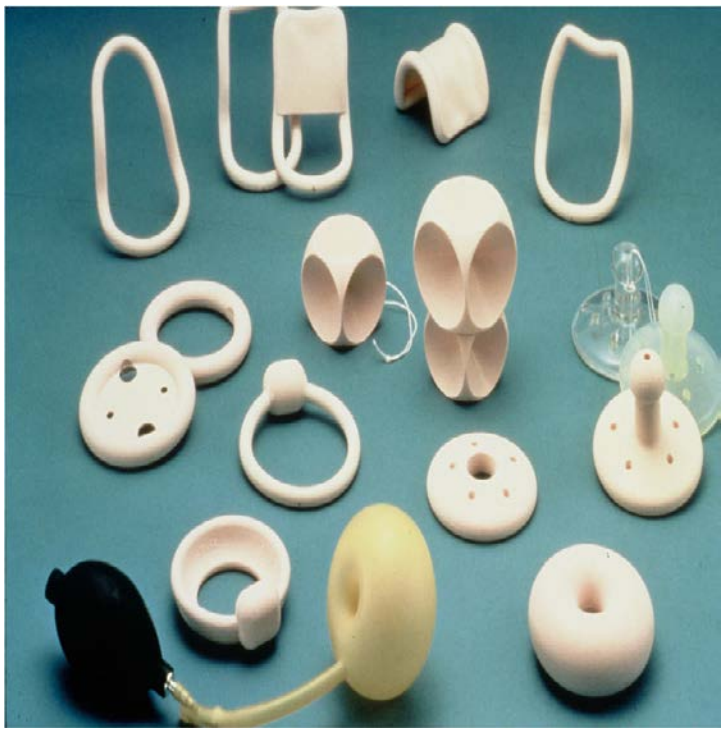


Figure 12-3 Different types of vaginal pessaries

Surgical therapy is the primary management for severe degree of POP. Main indications for surgical treatment are:

>Severe pain syndrome

- Failure of conservative treatment
- Presence of voiding problems or obstructive defecation
- Ulceration
- Recurrence of the prolapse
- Patients desire for surgical treatment

The type of the surgery should be individualized according to the patient's preference, lifestyle, age, contaminant diseases, and desire to the future fertility. There are following types of surgical treatment of POP:

-simple hysterectomy without reconstruction of the support abnormalities

-abdominal, laparoscopic, robotic sacrocolpoplexy and vaginal uterosacral suspension

-anterior and posterior vaginal surgery

-obliterative surgery, or total colpocleisis

-the transvaginal use of synthetic mesh (Figure 12-4)

-mid-urethral sling, Burch urethropexy in patients with urine incontinence

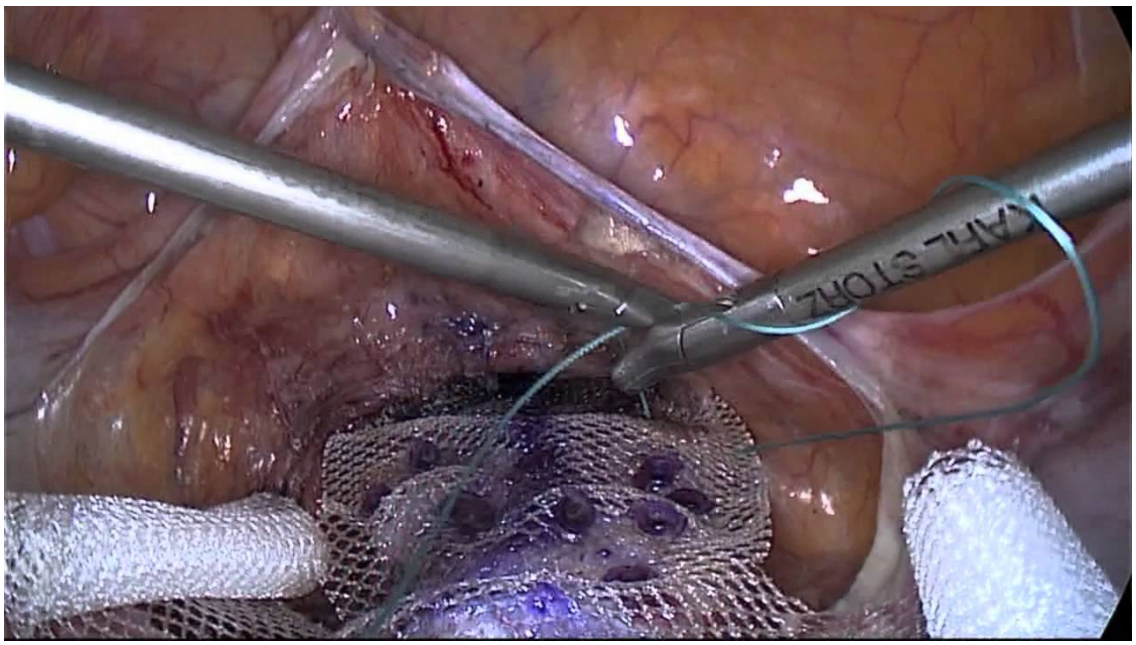


Figure 12-4 Using of special synthetic mesh for the treatment of uterine prolapse

Simple hysterectomy is insufficient for symptom resolution and high incidence of postoperative complications and recurrences. If the uterus presents hysterectomy with sacrispinous ligament suspension or uterosacral suspension is performed. Reconstructive surgery is recommended for those who would like to preserve sexual activity. The approach may be abdominal, laparoscopic, and robotic. Vaginal vault suspension, or colpoplexy, for apical prolapse is performed for fixation of the top of the vagina. So the vaginal vault is suspending to the sacrum, sacrospinous ligaments or uterosacral ligaments. The operation may be done abdominally or vaginally. Vaginal fixation of the vault to the sacrospinous ligament can be complicated by injury of the pudendal nerve and blood vessels.

Anterior and posterior colporrhaphy correct anterior or posterior vaginal wall prolapse and help to support the urethra and rectum appropriately. Anterior colporrhaphy involves plication of the pubocervical fascia to support the bladder and urethra. A rectocele can be repaired by levator plication or by repair of discrete fascial defects. In some cases a mesh may be placed in the posterior vaginal wall for additional support. The main postoperative complications are difficulty in voiding and recurrence of the prolapse.

Vaginal closure procedure, or colpocleisis, is performed in patients with advanced vaginal prolapse who no longer desire coital function and elderly women who are not likely to tolerate more invasive reparative surgery. The technique of operation includes suturing the partially denuded anterior and posterior vaginal walls together, that the uterus remains in situ and supported above the occluded vagina.

In the presence of urinary incontinence most commonly Burch colposuspension is performed. The goal of this procedure is to suspend and stabilize the urethra so that the urethrovesical junction and proximal urethra are replaced intraabdominally. Usually it is done in a laparoscopic approach. For patients with III type of stress urinary incontinence mid-urethral sling procedure is indicated. The main complications of these operations are voiding difficulty, urinary retention, development of urgency urinary incontinence, and vaginal wall prolapse.

Prevention of the POP includes identification and treatment of constipation, avoiding of power lifting, weight gain, treatment of

chronic respiratory diseases, and administration of estrogen to menopausal women.

Chapter review

1. What forms the layer of the pelvic floor between the endopelvic fascia and the urogenital diaphragm?

A) Levator ani

B) Vagina

C) Ishiocavernosus muscle

D) Pubococygeus muscle

E) Superficial transverse perineal muscle

2. What is the women's life time risk of surgery for genital organ prolapse?

A) 9-11%

B) 8%

C) 3-5%

D) 15%

E) 6-7%

3. Which of the followings is the most common type of POP?

A) Anterior vaginal wall prolapse

B) Upper posterior vaginal wall prolapse

C) Lower posterior vaginal wall prolapse

D) Apical prolapse

E) Total uterine prolapse

4. What are the main contributors to POP in menopausal women?

A) Hypoestrogenism and genital atrophy

B) Frequent urinary tract infections

C) Constipation and cystitis

D) Neuropathy

E) Weakness of the perineal muscles

5. Distal part of the prolapse locates 1 cm beyond the vaginal opening. Name the stage of the prolapse

A) Stage 3

B) Stage 1

C) Stage 2

D) Stage 0

E) Stage 4

6. Which of the following is the main method of diagnosis of POP?

A) Vaginal examination in a supine and standing position

B) Transvaginal ultrasound

C) Bimanual examination

D) Urodinamia

E) Laparoscopy

7. Which of the followings is not a symptom of anterior vaginal wall prolapse?

A) Difficulty of defecation

B) Frequent urination

C) Feeling of fullness in the vagina

D) Nocturia

E) Dysuria

8. Name types of conservative management of cystocele:

A) Pessaries, Kegel’s exercise, estrogens

B) Pessaries, Kegel’s exercise

C) Estrogens and Kegel’s exercise

D) Antibiotics, pessaries, estrogens

E) Antibiotics, pessaries

9. Which one is not the possible complication of pessary use?

A) Amenorrhea

B) Urinary retention

C) Vaginal ulceration

D) Abnormal vaginal discharge

E) Recurrent urinary infections

10. What should be the basis principle in the management of POP?

A) Individualization

B) Age of the patient

C) Degree of the prolapse

D) Socioeconomic factor

E) Fertility function

Chapter 13 Menopause

13.1 Endocrinology and Consequence of Estrogen Deficiency

Menopause is the period of woman’s life after the cessation of the functional activity of the ovaries. In view of the increased average life time of women the duration of menopause may reach 30-50 years. The preservation of quality of life, physical and mental activity is a high priority of menopausal women.

Literally, menopause is the cessation of menstrual cycles which has already lasted for at least 12 month. In most of cases is diagnosed retrospectively. The average time for menopause is age of 51, and that’s mean the end of the fertile phase of the woman’s life. In most women, menopause occurs between the ages of 50-55 years. Some women experience a natural menopause before age 40. This is considered premature. This condition may be hereditary predisposed, or induced by radiotherapy, chemotherapy, or following surgery on ovaries removal.

The “change of life” or “climacteric” refers to the period of woman’s life when a gradual decline in ovarian function results in decreasing of sex steroid production with subsequent hormonal changes. There are hormonal changes and symptoms caused by them in the years leading up to, and beyond the last menstrual cycle. Because climacteric is a normal physiologic process of aging, it should not be considered an endocrinopathy.

There was confirmed that the frequency of female population in climacteric period is high enough. By recommendation of WHO climacteric period is divided on perimenopase, menopause, and postmenopause. Perimenopause refers to the time preceeding menopause. Postmenopause comes after the cessation of climacteric symptoms, which may usually take place in 1-5 years. It is estimated that 25 million of women enters the postmenopause annually. To 2030 this number will increase to 1.2 billion.

The change in the quality and frequency of bleeding during the menstrual periods is a major sign of premenopause. About 10% of women experiences immediate amenorrhea, 70% shows symptoms of oligomenorrhea or hypomenorrhea, while 20% suffers from metrorrhagia or hypermenorrhea.

Despite large number of investigations, dedicated to the study of the climacteric period, the problem of hormonal changes and their sequel is still a concern. These hormonal alterations often result in severe and even harmful physical, psychological, and sexual changes in postmenopausal women and can have a negative impact on their quality of life, and increase the probability of different hyperplastic processes of reproductive organs, including neoplastic processes.

Menopause and related involutive processes of the reproductive organs are the result of hormonal changes of hypothalamo-pituitary-ovarian system. The changes start for some years before menopause, and display as anovulatory and irregular menstrual cycles, unopposed estrogen production, which results in endometrial hyperplasia,

emotional lability. These perimenopausal symptoms may last 3 to 5 years before complete interruption of the menses. Starting from age of 40 years serum level of FSH starts to increase, level of LH starts to increase from age 45 years. After menopause levels of these hormons dramatically increase in comparison with reproductive period indicators (LH 3 folds and FSH 14 folds, more than 35 IU/L). Low circulating estrogen levels by the negative feedback mechanism stimulate the hypothalamus to produce increased amount of GnRH and release it into the pituitary portal circulation. This leads to increased synthesis of FSH and LH.

During perimenopausal period processes of oocytes loss and primordial follicle atresia significantly accelerated. The number of granulesa and teka-cell layers in the follicles decreases. The regular avulatory cycles are replaced by the cycles with corpus luteum insufficiency or anovulatory cycles. Absence of corpus luteum following with significant decrease of progesterone level, results in endometrial hyperplasia and dysfunctional climacteric uterine bleedings. The minimal progesterone present is insufficient to induce the cytoplasmic enzymes to convert estradiol to the less potent estrone sulfate and to reduce the levels of cellular estrogen receptors. This process leads to increased estrogen-induced mitosis in the endometrium, and thus, to endometrial hyperplasia.

Some women continue to produce estrogens in small amounts even after menopause. Androstenedione from the ovary and the adrenal gland is converted in peripheric fat tissue to estrone. This fenomena is beneficial for women, and results in reducing the climacteric

symptoms, as swelling and hot flashes, incidence of osteoporosis, and atrophic processes of the genitalia. But unopposed estrogens may be responsible for the increased incidence of hyperplastic processes of the reproductive organs and breast.

The cessation in estradiol synthesis and prevalence of estrone are characteristic for postmenopause. The indicator of correlation of estradiol/estrone (E2/E1) is less than 1. The following criteria for postmenopausal hormones were determined:

- Low level of estradiol
- High level of FSH
- LH/FSH <1
- Indicator of E2/E1 correlation<1
- Possible hyperandrogenia
- Low level of inhibin

Postmenopausal hormonal changes are following by the series of vegetative-vascular, metabolic, endocrine, and psychological-emotional dysfunctions. Thus, adaptation to estrogens deficiency occurs. The incidence of climacteric symptoms is 40-80%.

The severity of climacteric syndrome is assessed by the Kupperman scale (Table 13.1-1)

MRS item	Scale		Corrected item-total correlation	Cronbach's alpha†
	Mean†	Variance†		
1. Hot flashes and sweating	14.61	67.98	0.65	0.78
2. Heart problems	15.56	68.91	0.57	0.79
3. Sleep problems	15.61	72.60	0.47	0.80
4. Feeling unhappy	15.86	71.97	0.54	0.79
5. Nervousness	15.30	66.38	0.68	0.78
6. Anxiety	15.41	68.96	0.57	0.79
7. Physical and mental fatigue	15.05	69.39	0.27	0.83
8. Sexual problems	16.36	75.74	0.39	0.80
9. Urinary problems	15.87	72.73	0.45	0.80
10. Vaginal dryness	16.42	76.60	0.36	0.81
11. Joint and muscle problems	14.81	71.73	0.49	0.79

MRS, Menopause rating scale.
†If item deleted.

Table 13.1-1 The Kupperman scoring system for climacteric syndrome

Loss of estrogen is associated with dystrophic and atrophic processes in the estrogen depending organs. The severity of these processes depends on the age, duration of the menopause, degree of estrogen deficiency, and metabolic failure. As the vagina, urethra, bladder have a common embryonic origin and develop from urogenital sinus, so they have receptors to estrogen, progesterone, and androgen. The general amount of these receptors is located in the mucous and muscular layers of the vagina, in the epithelial tissue of the muscular, vascular, and connective tissue of the urethra, detrusor, in the muscles of the perineal body, ligamentum teres uteri, and the pelvic connective tissue. The estrogen deficiency in the postmenopause leads to significant atrophic changes in these organs, and results in genital prolapse and urinary incontinence.

Most, but not all, symptoms of the menopause are directly related to fluctuating estrogen levels. But there are many symptoms associated

with the menopause, mainly caused by changes in the levels of estrogen in the body. But not every woman experiences these symptoms. The most common climacteric symptoms are:

-hot flashes

-anxiety

-depression

-irregular periods

-irritability

-urinary problems

-poor memory and concentration

-dryness of the vagina

-disrupted sleep

-osteoporosis

-cardiovascular diseases

-headache

-loosing of skin tone and alopecia

-joint and muscle pain

-weight gain

About 80% of women suffer from hot flashes. Approximately 40% of them experience hot flashes in a most distressing form. Flushes often

start around 47 or 48 years and usually continue for three of four years. 25% of women will have occasional flashes for more than 5 years. According to some studies, 9% of 72-year-old women suffer from hot flashes. Flashes may occur with the frequency every 30-40 minutes. Usually they associated with sweating, dizziness, and palpitations, sometimes disturbing the night sleep. The result of night flashes is increased incidence of irritability and fatique. One of the causes of disrupted sleep is anxiety. Climacteric depression is more often associated with early morning waking, following by tossing and turning until it is time to get up. As the climacteric hormonal changes may aggravate underlying anxiety and depression, specific medical therapy is necessary. Some women complain of confusion, loss of memory, lethargy, and inability to cope.

Fluctuating hormone levels can trigger migraine and other headaches in susceptible women. Rare menstrual cycles accompanied with more prominent premenstrual syndrome. Headaches usually improve with the cessation of the hormonal fluctuations in postmenopause.

Menopausal loss of estrogen reflects the condition of the skin and hair. Estrogens support skin collagen synthesis, keep it moisturized and stimulate hair growth. Without estrogen skin becomes dry, loose it tone, wrinkles appear. Hair growth restricted, but hair loss stays the same, so it results in hair thinning. As metabolism and energy burn become more slowly in the menopause, it follow by weight gain and settling of the fat in the waist and upper back area.

Although the climacteric symptoms are not life threatening, the long-term estrogen deficiency may be. The major diseases of late postmenopause are heart disease, strokes, breast and bowel cancer, osteoporosis, and dementia. All these consequences of menopause signifiycantly affect the quality of life, so treatment and prevention of these conditions are the high priority.

13.2 Osteoporosis

Osteoporosis is a systemic disease of the bone tissue, which characterizes by the decreasing of the bony mass and remodeling of the bones with predomination of the osteoclasts, what result in increased bone fragility, and thus increasing risk of fractures.

Incidence of postmenopausal osteoporosis in developed countries is 25-40%. A rate of bone fracture among women older than 50 years is increased by a factor of fourfold to sixfold. The most characteristic manifestations of the climacteric osteoporosis are fractures of spinal column, neck of the femoral bone, and radial bone in the typical locations. That’s mean the loss of the calcium generally from the trabecular bones. (Figure 13.2-1)

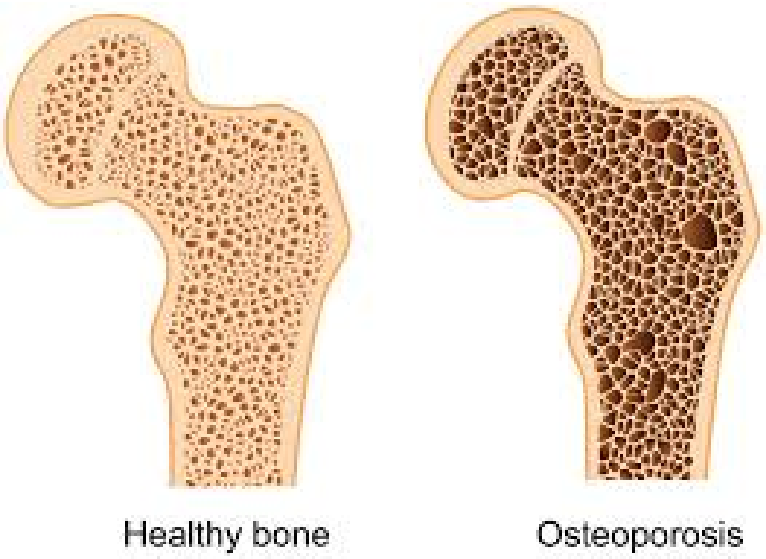


Figure 13.2-1 Demineralisation of bone during osteoporosis

Osteoporosis is a very serious social-economic problem, decreasing the quality of life, and being the cause of disability and premature death.

The mechanism of influence of the sex steroids to the bone tissue is complex and not clearly known. In 1988 two independent groups of scientist found out estrogen receptors in the osteoblasts. But later estrogen receptors also were found in osteoclasts, bone endothelial cells, osteocytes and other bone cells. The deficiency of the sex hormones I the menopause lead to acceleration of the bone metabolism with predomination of the bone resorption. Decreasing of calcium absorbtion in the intestines and D vitamin deficiency result in negative calcium balance, which leads to secondary hyperparathyroidism and increasing of bone resorption. Thus, predomination of bone resorption over the bone formation on the background of sex hormone deficiency is one of the pathogenetic mechanisms of postmenopausal osteoporosis.

Risk factors for osteoporosis include:

-females

-family history of osteoporosis

-ethnicity (white or Asian ethnic group)

-advanced age

-delayed menarche

-early menopause

-slender body composition

-infertility

-alcohol consumption

-smoking

-use of corticosteroid and anticonvulsant medications

-intolerance to the dairy products

Osteoporosis usually has asymptomatic duration, so early diagnosis is difficult. Most commonly the initial clinical symptom of osteoporosis is a fracture, which usually occurs in a minimal trauma.

There is recommended mineral bone density screening for osteoporosis in women of risk group who are 50 years or older, and women without risk factor who are 65 years and older. The gold standard for screening is dual-energy x-rays absorptiometry (DEXA). The results of this examination are expressed in T scores, which are standard deviations (SDs) from the peak bone mineral density of normal young adults.

Osteoporosis is defined as T score of less than -2.5 SD. Densitomety is used for both diagnosis of osteoporosis and osteopenia.

Treatment of osteoporosis is symptomatic and pathogenetic. For reducing the risk for osteoporosis there are recommendations for changing dietary habits and lifestyle. Postmenopausal women should consume 1200 to 1500 mg of calcium and 400-600 U of vitamin D, which are contained in 2-3 portions of dairy products, or vitamin D supplements. Patient should avoid smoking and alcohol consumption increase physical activity, as walking and weight-bearing exercises. (Figure 13.2-2)

Figure 13.2-2 Products rich with Calsium recommended for prevention of osteoporosis

Medical treatment is directed to the diminishing of resorption processes in bones and includes:

1. Hormonal replacement therapy by estrogen (HRT)
2. Calcitonin
3. Bisphosphonates
4. Selective estrogen receptor modulators (SERMs)

Decision about HRT depends on presence of risk factors for osteoporosis. Oral, transdermal, vaginal, intracutaneous, intramuscular administration of HRT is used. Before the administration of HRT mammography, genital ultrasound, cervical cytology, and DEXA are necessary. There was confirmed that combined estrogen-progestin therapy reduces incidence of postmenopausal fractures by 24% compared with controls. (Table 13.2-1)

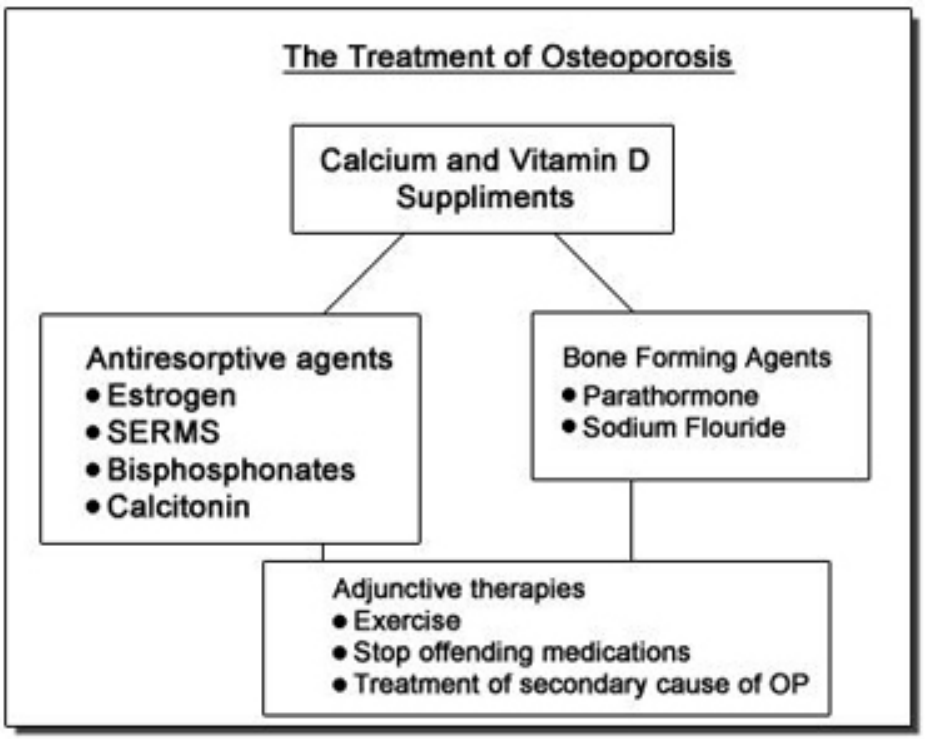


Table 13.2-1 Algorithm for treatment of osteoporosis

Administration of calcitonin depresses bone resorption, stimulates formation of bone, increases mineral density and improves quality of bones. According to the WHO investigations, calcitonin using for treatment of osteoporosis decreases incidence of spinal column fracture to 55% and femoral neck to 66%. Intramuscular injections and nasal sprays are available.

Studies have shown that administration of SERMs for treatment of osteoporosis is beneficial for the prevention of vertebral fractures, however in prevention of hip fracture they are nor successful.

Randomized placebo-controlled clinical trials have shown that bisphosphonates reduce vertebral fracture risk in postmenopausal women with osteoporosis. Biphosphonates are highly effective at limiting the loss of bone mass, deterioration of bone microarchitecture, and increased fracture risk that occur with aging. Although they are generally well tolerated, potential adverse effects, such as gastroesophageal irritation, osteonecrosis of the jaw, severe suppression of bone turnover may limit bisphosphonate use in some patients.

Prevention of osteoporosis is very important. It is include special well-balanced diet high in calcium and vitamin D, weight-bearing exercises, such as walking, hiking, jogging, climbing stairs, dancing, improving of lifestyle, so quit smoking and limit alcohol intake, and early screening.

13.3 Hormonal Replacement Therapy

With the increase in life time of women the duration of menopause increases as well. So the guarantee of the quality of life and prevent some diseases in postmenopause is one of the priority issues of modern gynecology. It was proved that HRT decreases incidence of female mortality generally because of beneficial effect on cardio-vascular system. HRT is the most effective treatment for the symptoms of estrogen deficiency.

The first documented prescription for HRT was in 1896 by a German gynecologist for 23-year-old woman after surgical ovaries removal. After successful manufacturing of synthetic estrogen in 1930 HRT was born. But widespread use of estrogen starts in 1960 after the publishing of Robert Wilson's best-seller "Feminine Forever", which demonstrated estrogen as a panacea for all the effects of aging. This results in increased incidence of endometrial cancer in the middle of 70^{th}. To correct this side effect of unopposed estrogen progestogen was combined with the estrogen. So, combined estrogen/progestogen therapy is recommended for menopausal women with a uterus. Later, studies revealed a specific benefit of HRT for preventing of long-term consequences of estrogen deficiency as osteoporosis, heart attack, stroke, Alzheimer's disease. (Table 13.3-1)

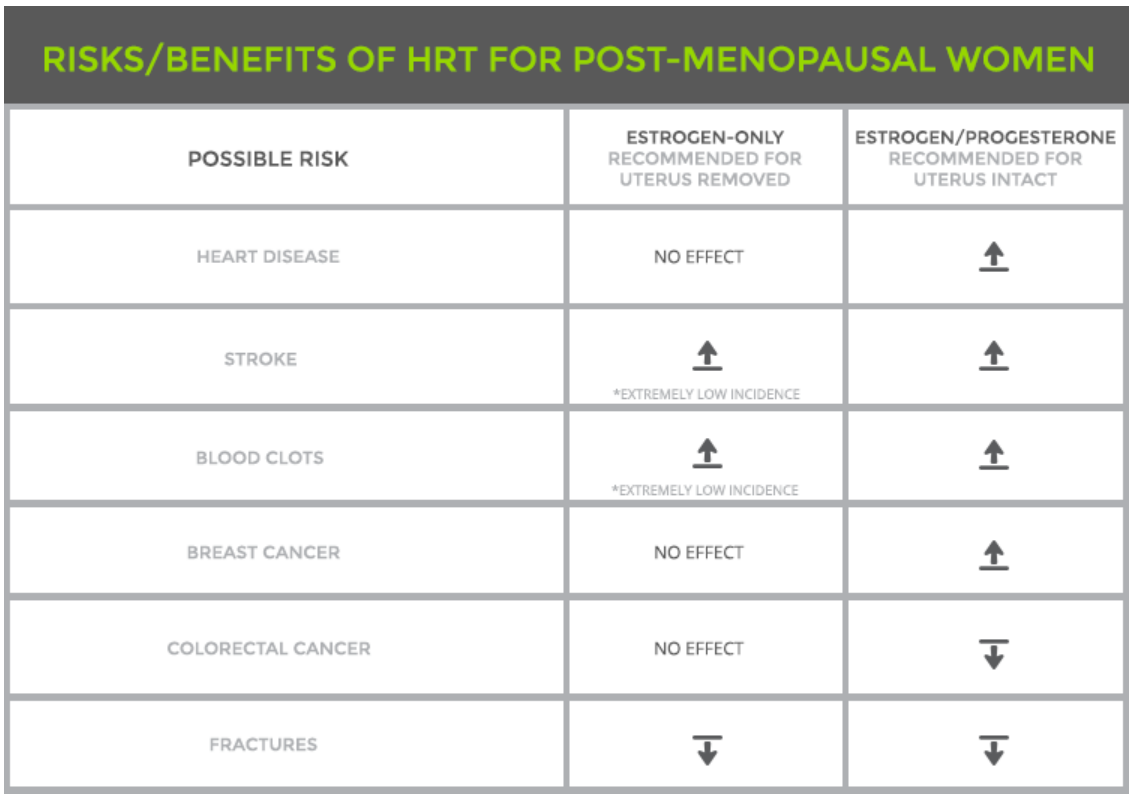


Table 13.3-1 Risks and benefits of HRT for post-menopausal women

There were several studies attempted to sort out the risk and benefits of HRT. But in deciding whether to take HRT, it is important to consider of the benefits and risks for each personal situation:

-age

-type of HRT taken-estrogen only or estrogen/progestogen

-ways of administration-oral or transdermal

-dose of HRT

-time of menopause

-personal medical history

-family history

Numerous studies confirmed that combined HRT is beneficial in relief of significant menopausal symptoms such as frequent hot flashes, genitourinary discomfort, prevention of risk of osteoporosis, increasing incidence of colorectal cancer and arthritis. Women who undergo premature menopause are at particular risk of developing osteoporosis and heart disease. Administration of HRT in this group of women showed positive outcomes and no evidence of increased risk of breast cancer, heart disease and stroke compared with menstruated women with a normally timed menopause.

HRT is highly effective in relieving the symptoms of the menopause. Therapy with lowest dose of estrogen improves hot flushes and night sweats within a few weeks of starting treatment. It is important gradually to reduce HRT over two or three month to assess the return of any symptoms. If HRT is stopped too quickly flushes and sweats will return just because of the sudden drop in hormone levels.

HRT influence atrophic processes of the genitourinary tract. It improves vaginal cytology, decreases pH, stimulates blood supply of the pelvic organs, and changes quality of the vaginal mucus. Vaginal dryness or soreness and urinary frequency and urgency may take longer to respond. The better therapeutic effect is obtained at intravaginal administration of HRT.

HRT for prevention of osteoporosis in menopause should start as early as possible before the architecture of the bones is not destroyed. Daily dose of estrogen equal to 0.625 mg/day depresses the resorption and decreases speed of bone mass loss. Incidence of osteoporotic

fracture is reduced to 20-60%. Protective effect of HRT on incidence of femoral neck fracture increased, especially in women of slender body constitution and low physical activity. Recent studies show that combined therapy with estrogen and bisphosphonates is more effective than isolated administration of estrogen. But need for prevention and treatment of osteoporosis may be determined by bone densitometry studies, and therapy with bisphosphonates and reloxifene is the first line treatment in the absence of significant menopausal symptoms. Significant role of estrogen in maintenance of periodontal tissues was confirmed.

Colorectal cancer is one of the most common types of cancer among postmenopausal women with high mortality rates. HRT significantly decreases incidence of colorectal cancer, approximately 37%. The mechanism of this protective effect of estrogen is not clearly known. Depression of the oncotic activity through the colorectal receptors and interfere of estrogens with the metabolism of bile acids are suggested.

Increasing evidence suggests that HRT reduces the symptoms of arthritis, although it is licensed for this indication. This is true for both osteoarthritis and rheumatoid arthritis. It is recommended to adjunct HRT to conventional therapy, as it does not reverse the process of these conditions.

Global investigations revealed positive influence of estrogen on function of neurons. They decrease collection of the amyloid in the brain tissue, and increase holinergical activity that most relevant in

relation to the risk of Alzheimer's disease. The risk of Alzgeimer's disease decreases to 40-60% and directly proportional to the duration of estrogen therapy. Estrogens also improve memory, mood, quality of life, while progestogens weaken some of these effects.

It is known that loss of estrogen levels in postmenopause leads to developing of heart diseases, which are the leading cause for female mortality. HRT decreases the risk for heart diseases to 30-50%. Protective effect of estrogen is caused by it influence on the cholesterol metabolism, carbohydrate metabolism, aterogenez and hemodynamics. But, observational studies have raised concern about HRT and the risk for venous thrombosis and pulmonary embolism. If patient have multiple risk factors for venous thrombosis, such as severe varicose veins, genetic risk factor for thrombosis as factor V Leiden, obesity, increased age, inactivity, high blood pressure and diabetes mellitus, HRT is probably best avoided.

There appears to be a small increase in the risk of ovarian cancer in women using HRT. Studies show that one extra woman out of 2500 women using HRT over 5 years will develop ovarian cancer compared with a similar group of women not taking HRT. The incidence of endometrial cancer increases sixfold in women taking monotherapy with estrogen. HRT with combined estrogen/progestogens reduces risk of endometrial cancer to 0.9% comparing with incidence of endometrial cancer in women not taking HRT.

HRT is considered one of the risk factors for breast cancer. That's why many patients avoid using of HRT for relief the climacteric symptoms. There were several studies regarding risk of HRT for breast cancer. The most global is Beral's investigation, which involved data about 52702 women without and 108411 women with breast cancer. So, the analysis of the results of study show increased incidence of breast cancer among women using HRT during last 1-4 years, with increasing of incidence on 2.3% for each year of therapy. There were some interesting findings: HRT didn't increase incidence for breast cancer in women with hereditary predisposition to breast cancer, and incidence of breast cancer didn't increase within 5 years after cessation of HRT. But the prognosis of breast cancer on the background of HRT was more favorable comparing with cancer without HRT. And mortality rates of breast cancer associated with HRT were decreased.

There are many different types of HRT. Women, who have had a hysterectomy, may be administrated estrogen therapy only. Estrogens used in HRT are either natural or synthetic. Natural estrogens are similar in chemical structure to the estrogens produced by ovaries, whereas synthetic estrogens have a different structure. Most common estrogens used for HRT are Equilin and 17-alfadihidroequilin are natural estrogens derived from the urine of pregnant mares, and dienoestrol, ethinylestradiol and mestranol are synthetic estragens. (Table 13.3-2)

Medication	Post-Menopausal Replacement Dose	Gender Reassignment Dose
Conjugated Equine Estrogens (*Premarin*)	0.625 mg PO qd	Starting: 1.25-2.5 mg PO qd Average: 5 mg PO qd Maximum: 10 mg PO qd
Ethinyl Estradiol (*Estinyl*)	0.05 mg PO qd	Starting: 0.1-0.2 mg PO qd Average: 0.4 mg PO qd Maximum: 0.5 mg PO qd
Estradiol (*Estrace, Gynodiol*)	0.5 mg PO qd	Starting: 1-2 mg PO qd Average: 4 mg PO qd Maximum: 5 mg PO qd
Estradiol Valerate injection (*Delestrogen*)	10 mg IM q2wks	Starting: 20-40 mg IM q2wks Average: 40 mg IM q 2wks Maximum: 40-60 mg IM q2wks
Estradiol patch (*Alora, Climera, Esclim, Estraderm, Vivelle, Vivelle-Dot*)	0.05 mg/d dermal (change 0.5-1.0 mg patches once-twice/week)	Starting: 0.1-0.2mg/d Average: 0.2-0.3mg/d Maximum: 0.3mg/d

Figure 13.3-2 Recommended rejimen of HRT for post-menopausal women

Synthetic estrogens are more potent and so more favorable for contraception. Estrogens are available in different forms: tablets, patches, creams, pessaries, vaginal rings. (Figure 13.3-1)

Figure 13.3-1 Various types of estrogens for HRT

Women who still have a uterus should be treated by combined estrogen/progestin medicines or concurrent progestin, because of great risk for endometrial hyperplasia and endometrial adenocarcinoma as a result of stimulating effect of unopposed estrogen. Concurrent progestin may be given for 10-14 days per month, what mimics the natural menstrual cycle in which progesterone produces for the last 14 days. Patients with complete menopausal amenorrhea should be given continuous combined estrogen/progestin. Natural and synthetic progesterone is available. Progestin preparations as tablets, vaginal gel, suppositories and intrauterine device are exist.

For patients with only complain on genitourinary symptoms local administration of estrogen as vaginal cream, tablets, or rings indicated. Use of progestin in these cases is not necessary.

Administration of HRT may be cyclical or continuous. HRT is usually started around the menopause in order to control hot flashes and sweats. But the time to start HRT depends on personal circumstances of the patient after balancing all benefits and risks. Duration of HRT may take up to 5 years. However, long-term use can be associated with increased risk of breast cancer, venous thrombosis and stroke. Some women wish to continue HRT lifelong, just because it makes them feel so well.

With proper counseling, appropriate screening, improving of lifestyle, and professional care, climacteric symptoms can be managed

successfully. Future research will help further to improve HRT, eliminate side effect, and find new safe and more effective alternatives for HRT.

Chapter review

1. Literally, definition of menopause is absent of menstruation after the final period within the period of time :

A) 12 month
B) 6 month
C) 2 years
D) 15 month
E) 5 years

2. The average age for menopause is:

A) 51 year
B) 45 year
C) 55 year
D) 48 year
E) 60 year

3. The menopausal blood indicator of FSH is:

A) Greater than 35 IU/L
B) Less than 35 IU/L
C) 10 IU/L
D) 5 IU/L

E) Less than 20 IU/L

4. What is the primary source of estrogen in postmenopausal women?

A) Peripheral conversion of adrenal and ovarian androgens by aromatization

B) Ovarian estradiol

C) Exogenous estrogens

D) Estradiol from extragonadal sites

E) Phytoestrogens

5. In what type of bone osteoporosis is more prevalent?

A) Trabecular bone

B) Flat bone

C) Short bone

D) Sesamoid bone

E) Irregular bone

6. Which of the following is not a risk factor for osteoporosis?

A) Weight-bearing exercises

B) Ethnicity

C) Advanced age

D) Smoking

E) Family history of osteoporosis

7. In which indicators of T score osteoporosis is defined?

A) Less than -2.5 SD

B) More than -2.5 SD

C) More than -1SD

D) T equal to 0.0SD

E) More than 0.0SD

8. Which of the following is not a risk of HRT?

A) Femoral fracture

B) Heart disease

C) Stroke

D) Breast cancer

E) Tromboembolic disease

9. HRT is not beneficial for reducing incidence of:

A) Breast cancer

B) Hot flashes and sweating

C) Colorectal cancer

D) Osteoporosis

E) Urogenital problems

10. What daily dose of estrogen depresses bone resorption and decreases speed of bone mass loss?

A) 0.625 mg

B) 0.25 mg

C) 1 g

D) 0.5 mg

E) 3 g

Chapter 14 Family Planning and Contraception

Optimization of maternal health and fetal well-being by allowing couples to plan and prepare for the pregnancies they desire is the main issue of family planning. Age peculiarities of female organism have a great importance in selection of reliable, safe and available methods of protection from both undesired pregnancy and variety of diseases, especially diseases of the reproductive system. Thus, contraception is one of the main factors, which help to preserve woman's health from puberty till menopause.

At the present precocious puberty is more evident comparing with previous generations. So, adolescents start sexual life; even have multiple partners before the onset of psychological and emotional maturity. Sometimes it results in unintended pregnancy, early maternity, disability of marriage, and increased number of abandoned children. In majority of cases unintended pregnancies terminated by abortions, which may be complicated by infertility, inflammatory diseases of reproductive organs, failure of menstrual cycle, psychological stress, and other gynecological diseases. 600000 women worldwide die from pregnancy and pregnancy-related conditions, and 3 million women suffer from permanent disabilities annually.

Series of studies of recent years show, that despite the certain knowledge about modern methods of contraception (94.6% of married women of

age 15-49 years heard about contraception), only 32% of women are using them. It was confirmed that 41% of all pregnancies in women of age 15-49 years result with abortions. This indicator changes with age groups:

- 20 years and earlier-8.7%

-20-24 years-21.4%

-25-34 years-44.3%

-35-44 years- 73.4%

But official statistics on abortions shows that only 2-2.5% of pregnancies terminate with abortions.

Incidence of sexually transmitted infections also significantly increases and may lead to unpredictable consequences for subsequent generations.

In connection with the above main goal of modern contraception is:

1. Prevention of abortions and unintended early births
2. Prevention of sexually transmitted infections

The safety of all methods of family planning is well established. The World Health Organization has developed its Medical Eligibility Criteria, which rates the appropriateness of each major contraceptive method in a variety of medical circumstances. Recommendations are made on 1 to 4 scales, in which a rating of 1 indicates approval and 4 represents an absolute contraindication. (Table 14.1-1)

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

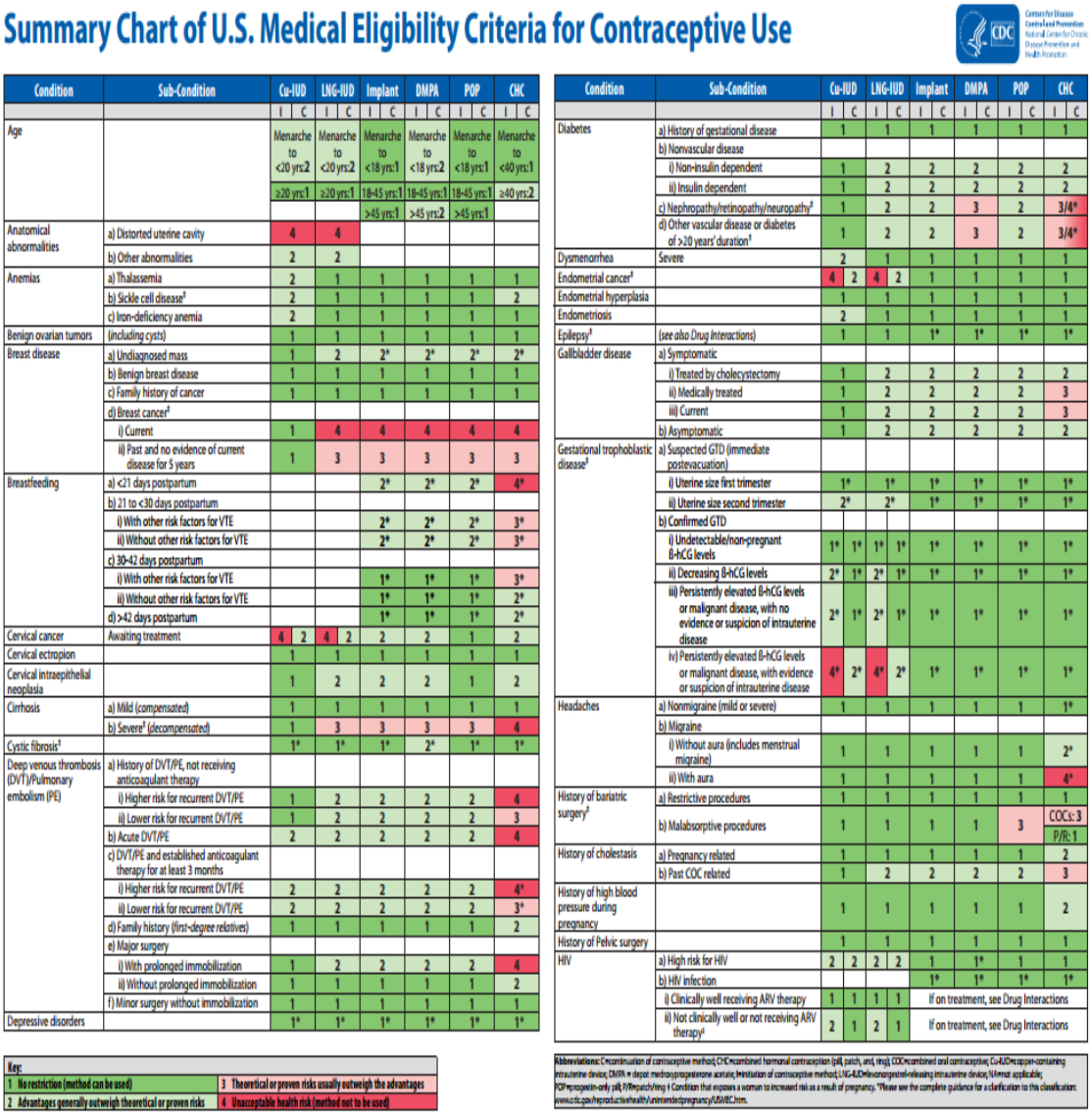
Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Age		Menarche to <20 yrs:2		Menarche to <20 yrs:2		Menarche to <18 yrs:1		Menarche to <18 yrs:2		Menarche to <18 yrs:1		Menarche to <40 yrs:1	
		≥20 yrs:1		≥20 yrs:1		18-45 yrs:1		18-45 yrs:1		18-45 yrs:1		≥40 yrs:2	
						>45 yrs:1		>45 yrs:2		>45 yrs:1			
Anatomical abnormalities	a) Distorted uterine cavity	4		4									
	b) Other abnormalities	2		2									
Anemias	a) Thalassemia	2		1		1		1		1		1	
	b) Sickle cell disease[†]	2		1		1		1		1		2	
	c) Iron-deficiency anemia	2		1		1		1		1		1	
Benign ovarian tumors	*(including cysts)*	1		1		1		1		1		1	
Breast disease	a) Undiagnosed mass	1		2		2*		2*		2*		2*	
	b) Benign breast disease	1		1		1		1		1		1	
	c) Family history of cancer	1		1		1		1		1		1	
	d) Breast cancer[‡]												
	i) Current	1		4		4		4		4		4	
	ii) Past and no evidence of current disease for 5 years	1		3		3		3		3		3	
Breastfeeding	a) <21 days postpartum					2*		2*		2*		4*	
	b) 21 to <30 days postpartum												
	i) With other risk factors for VTE					2*		2*		2*		3*	
	ii) Without other risk factors for VTE					2*		2*		2*		3*	
	c) 30-42 days postpartum												
	i) With other risk factors for VTE					1*		1*		1*		3*	
	ii) Without other risk factors for VTE					1*		1*		1*		2*	
	d) >42 days postpartum					1*		1*		1*		2*	
Cervical cancer	Awaiting treatment	4	2	4	2	2		2		1		2	
Cervical ectropion		1		1		1		1		1		1	
Cervical intraepithelial neoplasia		1		2		2		2		1		2	
Cirrhosis	a) Mild *(compensated)*	1		1		1		1		1		1	
	b) Severe[‡] *(decompensated)*	1		3		3		3		3		4	
Cystic fibrosis[‡]		1*		1*		1*		2*		1*		1*	
Deep venous thrombosis (DVT)/Pulmonary embolism (PE)	a) History of DVT/PE, not receiving anticoagulant therapy												
	i) Higher risk for recurrent DVT/PE	1		2		2		2		2		4	
	ii) Lower risk for recurrent DVT/PE	1		2		2		2		2		3	
	b) Acute DVT/PE	2		2		2		2		2		4	
	c) DVT/PE and established anticoagulant therapy for at least 3 months												
	i) Higher risk for recurrent DVT/PE	2		2		2		2		2		4*	
	ii) Lower risk for recurrent DVT/PE	2		2		2		2		2		3*	
	d) Family history *(first-degree relatives)*	1		1		1		1		1		2	
	e) Major surgery												
	i) With prolonged immobilization	1		2		2		2		2		4	
	ii) Without prolonged immobilization	1		1		1		1		1		2	
	f) Minor surgery without immobilization	1		1		1		1		1		1	
Depressive disorders		1*		1*		1*		1*		1*		1*	

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Diabetes	a) History of gestational disease	1		1		1		1		1		1	
	b) Nonvascular disease												
	i) Non-insulin dependent	1		2		2		2		2		2	
	ii) Insulin dependent	1		2		2		2		2		2	
	c) Nephropathy/retinopathy/neuropathy[‡]	1		2		2		3		2		3/4*	
	d) Other vascular disease or diabetes of >20 years' duration[‡]	1		2		2		3		2		3/4*	
Dysmenorrhea	Severe	2		1		1		1		1		1	
Endometrial cancer[‡]		4	2	4	2	1		1		1		1	
Endometrial hyperplasia		1		1		1		1		1		1	
Endometriosis		2		1		1		1		1		1	
Epilepsy[‡]	*(see also Drug Interactions)*	1		1		1*		1*		1*		1*	
Gallbladder disease	a) Symptomatic												
	i) Treated by cholecystectomy	1		2		2		2		2		2	
	ii) Medically treated	1		2		2		2		2		3	
	iii) Current	1		2		2		2		2		3	
	b) Asymptomatic	1		2		2		2		2		2	
Gestational trophoblastic disease[‡]	a) Suspected GTD (immediate postevacuation)												
	i) Uterine size first trimester	1*		1*		1*		1*		1*		1*	
	ii) Uterine size second trimester	2*		2*		1*		1*		1*		1*	
	b) Confirmed GTD												
	i) Undetectable/non-pregnant ß-hCG levels	1*	1*	1*	1*	1*		1*		1*		1*	
	ii) Decreasing ß-hCG levels	2*	1*	2*	1*	1*		1*		1*		1*	
	iii) Persistently elevated ß-hCG levels or malignant disease, with no evidence or suspicion of intrauterine disease	2*	1*	2*	1*	1*		1*		1*		1*	
	iv) Persistently elevated ß-hCG levels or malignant disease, with evidence or suspicion of intrauterine disease	4*	2*	4*	2*	1*		1*		1*		1*	
Headaches	a) Nonmigraine (mild or severe)	1		1		1		1		1		1*	
	b) Migraine												
	i) Without aura (includes menstrual migraine)	1		1		1		1		1		2*	
	ii) With aura	1		1		1		1		1		4*	
History of bariatric surgery[‡]	a) Restrictive procedures	1		1		1		1		1		1	
	b) Malabsorptive procedures	1		1		1		1		3		COCs: 3 P/R: 1	
History of cholestasis	a) Pregnancy related	1		1		1		1		1		2	
	b) Past COC related	1		2		2		2		2		3	
History of high blood pressure during pregnancy		1		1		1		1		1		2	
History of Pelvic surgery		1		1		1		1		1		1	
HIV	a) High risk for HIV	2	2	2	2	1		1*		1		1	
	b) HIV infection							1*		1*		1*	
	i) Clinically well receiving ARV therapy	1	1	1	1	If on treatment, see Drug Interactions							
	ii) Not clinically well or not receiving ARV therapy[‡]	2	1	2	1	If on treatment, see Drug Interactions							

Key:	
1 No restriction (method can be used)	3 Theoretical or proven risks usually outweigh the advantages
2 Advantages generally outweigh theoretical or proven risks	4 Unacceptable health risk (method not to be used)

Abbreviations: C=continuation of contraceptive method; CHC=combined hormonal contraception (pill, patch, and, ring); COCs=combined oral contraceptive; Cu-IUD=copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; I=initiation of contraceptive method; LNG-IUD=levonorgestrel-releasing intrauterine device; NA=not applicable; POP=progestin-only pill; P/R=patch/ring. ‡ Condition that exposes a woman to increased risk as a result of pregnancy. *Please see the complete guidance for a clarification to this classification: www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm.



Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Condition	Sub-Condition	Cu-IUD I	Cu-IUD C	LNG-IUD I	LNG-IUD C	Implant I	Implant C	DMPA I	DMPA C	POP I	POP C	CHC I	CHC C
Age		Menarche to <20 yrs:2		Menarche to <20 yrs:2		Menarche to <18 yrs:1		Menarche to <18 yrs:2		Menarche to <18 yrs:1		Menarche to <40 yrs:1	
		≥20 yrs:1		≥20 yrs:1		18-45 yrs:1		18-45 yrs:1		18-45 yrs:1		≥40 yrs:2	
						>45 yrs:1		>45 yrs:2		>45 yrs:1			
Anatomical abnormalities	a) Distorted uterine cavity	4		4									
	b) Other abnormalities	2		2									
Anemias	a) Thalassemia	2		1		1		1		1		1	
	b) Sickle cell disease[2]	2		1		1		1		1		2	
	c) Iron-deficiency anemia	2		1		1		1		1		1	
Benign ovarian tumors	(including cysts)	1		1		1		1		1		1	
Breast disease	a) Undiagnosed mass	1		2		2*		2*		2*		2*	
	b) Benign breast disease	1		1		1		1		1		1	
	c) Family history of cancer	1		1		1		1		1		1	
	d) Breast cancer[2]												
	i) Current	1		4		4		4		4		4	
	ii) Past and no evidence of current disease for 5 years	1		3		3		3		3		3	
Breastfeeding	a) <21 days postpartum					2*		2*		2*		4*	
	b) 21 to <30 days postpartum												
	i) With other risk factors for VTE					2*		2*		2*		3*	
	ii) Without other risk factors for VTE					2*		2*		2*		3*	
	c) 30-42 days postpartum												
	i) With other risk factors for VTE					1*		1*		1*		3*	
	ii) Without other risk factors for VTE					1*		1*		1*		2*	
	d) >42 days postpartum					1*		1*		1*		2*	
Cervical cancer	Awaiting treatment	4	2	4	2	2		2		1		2	
Cervical ectropion		1		1		1		1		1		1	
Cervical intraepithelial neoplasia		1		2		2		2		1		2	
Cirrhosis	a) Mild (compensated)	1		1		1		1		1		1	
	b) Severe[4] (decompensated)	1		3		3		3		3		4	
Cystic fibrosis[3]		1*		1*		1*		2*		1*		1*	
Deep venous thrombosis (DVT)/Pulmonary embolism (PE)	a) History of DVT/PE, not receiving anticoagulant therapy												
	i) Higher risk for recurrent DVT/PE	1		2		2		2		2		4	
	ii) Lower risk for recurrent DVT/PE	1		2		2		2		2		3	
	b) Acute DVT/PE	2		2		2		2		2		4	
	c) DVT/PE and established anticoagulant therapy for at least 3 months												
	i) Higher risk for recurrent DVT/PE	2		2		2		2		2		4*	
	ii) Lower risk for recurrent DVT/PE	2		2		2		2		2		3*	
	d) Family history (first-degree relatives)	1		1		1		1		1		2	
	e) Major surgery												
	i) With prolonged immobilization	1		2		2		2		2		4	
	ii) Without prolonged immobilization	1		1		1		1		1		2	
	f) Minor surgery without immobilization	1		1		1		1		1		1	
Depressive disorders		1*		1*		1*		1*		1*		1*	

Condition	Sub-Condition	Cu-IUD I	Cu-IUD C	LNG-IUD I	LNG-IUD C	Implant I	Implant C	DMPA I	DMPA C	POP I	POP C	CHC I	CHC C
Diabetes	a) History of gestational disease	1		1		1		1		1		1	
	b) Nonvascular disease												
	i) Non-insulin dependent	1		2		2		2		2		2	
	ii) Insulin dependent	1		2		2		2		2		2	
	c) Nephropathy/retinopathy/neuropathy[2]	1		2		2		3		2		3/4*	
	d) Other vascular disease or diabetes of >20 years' duration[2]	1		2		2		3		2		3/4*	
Dysmenorrhea	Severe	2		1		1		1		1		1	
Endometrial cancer[2]		4	2	4	2	1		1		1		1	
Endometrial hyperplasia		1		1		1		1		1		1	
Endometriosis		2		1		1		1		1		1	
Epilepsy[3]	(see also Drug Interactions)	1		1		1*		1*		1*		1*	
Gallbladder disease	a) Symptomatic												
	i) Treated by cholecystectomy	1		2		2		2		2		2	
	ii) Medically treated	1		2		2		2		2		3	
	iii) Current	1		2		2		2		2		3	
	b) Asymptomatic	1		2		2		2		2		2	
Gestational trophoblastic disease[3]	a) Suspected GTD (immediate postevacuation)												
	i) Uterine size first trimester	1*		1*		1*		1*		1*		1*	
	ii) Uterine size second trimester	2*		2*		1*		1*		1*		1*	
	b) Confirmed GTD												
	i) Undetectable/non-pregnant β-hCG levels	1*	1*	1*	1*	1*		1*		1*		1*	
	ii) Decreasing β-hCG levels	2*	1*	2*	1*	1*		1*		1*		1*	
	iii) Persistently elevated β-hCG levels or malignant disease, with no evidence or suspicion of intrauterine disease	2*	1*	2*	1*	1*		1*		1*		1*	
	iv) Persistently elevated β-hCG levels or malignant disease, with evidence or suspicion of intrauterine disease	4*	2*	4*	2*	1*		1*		1*		1*	
Headaches	a) Nonmigraine (mild or severe)	1		1		1		1		1		1*	
	b) Migraine												
	i) Without aura (includes menstrual migraine)	1		1		1		1		1		2*	
	ii) With aura	1		1		1		1		1		4*	
History of bariatric surgery[3]	a) Restrictive procedures	1		1		1		1		1		1	
	b) Malabsorptive procedures	1		1		1		1		3		COCs: 3 P/R: 1	
History of cholestasis	a) Pregnancy related	1		1		1		1		1		2	
	b) Past COC related	1		2		2		2		2		3	
History of high blood pressure during pregnancy		1		1		1		1		1		2	
History of Pelvic surgery		1		1		1		1		1		1	
HIV	a) High risk for HIV	2	2	2	2	1		1*		1		1	
	b) HIV infection							1*		1*		1*	
	i) Clinically well receiving ARV therapy	1	1	1	1	If on treatment, see Drug Interactions							
	ii) Not clinically well or not receiving ARV therapy[4]	2	1	2	1	If on treatment, see Drug Interactions							

Key:

1 No restriction (method can be used)	3 Theoretical or proven risks usually outweigh the advantages
2 Advantages generally outweigh theoretical or proven risks	4 Unacceptable health risk (method not to be used)

Abbreviations: C=continuation of contraceptive method; CHC=combined hormonal contraception (pill, patch, and, ring); COC=combined oral contraceptive; Cu-IUD=copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; I=initiation of contraceptive method; LNG-IUD=levonorgestrel-releasing intrauterine device; NA=not applicable; POP=progestin-only pill; P/R=patch/ring; † Condition that exposes a woman to increased risk as a result of pregnancy. *Please see the complete guidance for a clarification to this classification: www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm.

Table 14-1 World Health Organization Medical Eligibility for initiating contraception: absolute and relative contraindications

14.1 Contraception

The meaning of contraception is prevention of pregnancy. There are a number of different methods of contraception with their advantages and disadvantages. (Table 14.1-1) Considerations when choosing contraception should include accurate information about:

-effectiveness in pregnancy prevention

-health issues which may limit some choices

-ease of use

-side effects including changes to usual periods

-benefits other than contraception

-cost and availability

-reversibility

-protection against sexually transmitted infections

There are a lot of types of contraception but they classified into three main groups:

1. Barrier and behavioral methods
2. Hormonal contraceptives
3. Intrauterine contraceptives

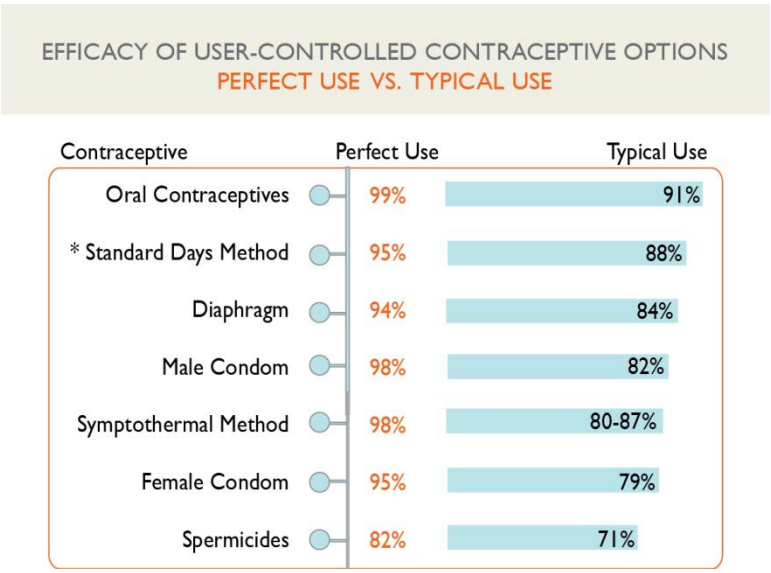


Table 14.1-1 Efficacy of contraceptive options

Barrier and behavioral contraceptives

The advantage of these methods of contraception is that they need to be used only at the moment of sexual intercourse. Unfortunately failure rates of these methods of contraception, especially behavioral methods, are very high. Barrier methods are the only methods of contraception which prevent sexually transmitted infections.

Behavioral methods of contraception include abstinence, withdrawal or coitus interraptus, physiologic contraception, as lactation, calendar method of contraception.

Abstinence or choosing not to have sex provides 100% protection from pregnancy and STIs. It is free and available for all. Withdrawal or coitus interraptus is the most effective behavioral method. The male move his penis away from the vagina before ejaculation. The goal of this method is to prevent sperm from entering the vagina. This method is effective, and pregnancy rate is approximately 4% with perfect use and 22 % with typical use. There may be entering of sperm into the vagina if the withdrawal isn't properly timed or pre-ejaculation fluid contains sperm. And withdrawal method doesn't protect from STIs.

The lactational amenorrhea method is a highly efficient tool for the individual woman to utilize physiology to space births. This method is based on three simultaneous conditions: 1) the baby is under 6 month; 2) the mother is still amenorrheic; and 3) she practices day and night breastfeeding. The failure rate of lactational amenorrhea, when breastfeed women have no menses for the first 6 month postpartum, is 2%. The lactational amenorrhea method is prudent to add another

method of contraception after 6 months, when it is no longer implemented.

Calendar method or fertility awareness method employ a variety of techniques to detect at-risk days. Once those days are identified, couples can practice periodic abstinence or use another barrier method of contraception. Before relying on this method, a woman records the number of days in each menstrual cycle for at least 6 months. The woman should subtract 18 from the length of her shortest recorded cycle to find out the estimated first day of her fertile time. Then subtracting 11 days from the length of her longest recorded cycle the estimated last day of her fertile time is detected. During the fertile time the couples should avoid sexual contact or use barrier or withdrawal methods of contraception. (Figure 14.1-1) The disadvantage of this method is a high rate of failure in preventing of pregnancy and STIs. This historical method has been replaced by other methods of natural family planning including urine tests that predict ovulation.

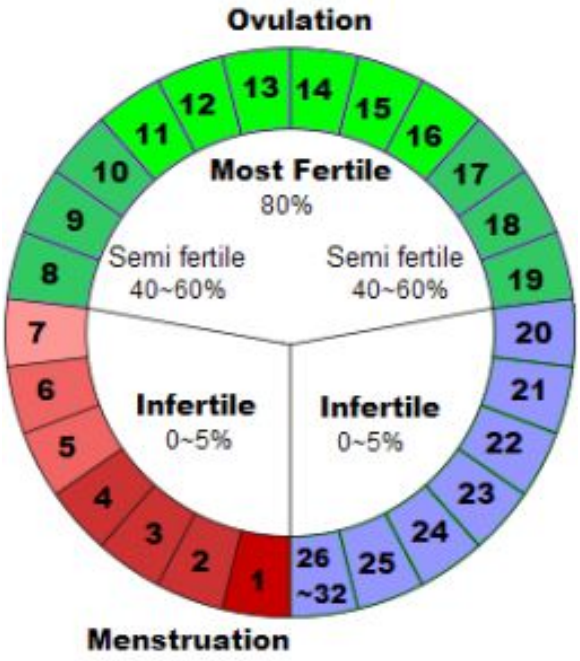


Figure 14.1-1 Demonstration of calendar method ofcontraception: fertile and infertile days of menstrual cycle

Barrier methods of contraception include:

-male condom

-female condom

-diaphragm

-spermicide

-sponge

-cervical cap

Barrier methods of contraception block sperm from entering the uterus and are used only during sexual intercourse. They do not affect woman's future fertility; they are safe for breastfeeding women, less expensive and available without a prescription. Condoms and diaphragms are effective in reduce the risk of STI and cervical cancer.

Male condoms have been available for many years, they are very effective, and have failure rate of 2%. The male condoms are usually made from latex, which have great potential to reduce all STIs. But with episodic use this protection is compromised. For couples with latex allergies polyurethane condoms are available. Male condoms are available in different sizes, shapes, textures, scent and flavors. Its effectiveness ranges from 88-95%. A male condom must be used early in sexual intercourse, because first drop of semen, which appears during

foreplay, contains millions of sperm that can result an unintended pregnancy.

Female barrier methods include diaphragms, a vaginal shield, a cervical cap, female condoms, and spermicides. Female condoms are made from polyurethane; they are lightly lubricated for easier use and consist of two rings that help to keep it in place inside the walls of the vagina. They must be inserted before sexual intercourse and used only once. Their efficiency is 95%. Diaphragm is a rubber thin device with a metal spring in the rim. It is inserted diagonally into the vagina, so across the front wall of the vagina covering the cervix during intercourse. Using a diaphragm with spermicide may increase risk of urinary tract infections. The cap is smaller and more rigid than a diaphragm and held in place by suction over the cervix. They are 85% effective.

Spermicides contain nonoxynol-9. They may cause the allergic reactions, develop sores in the vagina or on the penis, and irritate the lining of the vagina and rectum, thus increasing risk of STIs.

Hormonal contraceptives

Hormonal methods of birth control include estrogen and progestin containing pills, skin patches, vaginal rings, injections, and implants. (Figure 14.1-2)

Figure 14.1-2 Hormonal and barrier contraceptive methods

They act on gonadotropins secretion by blocking the luteinized hormone surge to prevent ovulation, thicken cervical mucus to prevent sperm from entering the uterus, and thin the lining of the uterus to prevent implantation. If they used correctly and continuously the failure rate is very low, about 0.3-2%.

Combined estrogen-progestin hormonal contraceptives are available in once-daily pills, once-a-week transdermal patches, and once-a-month vaginal rings. Hormonal pills are available in various estrogen-progestin combinations and doses. They come in packs. Most packs contain 3 weeks of hormone pills. Advantages of these pills are: protection against

pregnancy, regulation of heavy periods and dysmenorrhea, reduction of PMS, perimenopausal syndrome, decrease of a risk of endometrial and ovarian cancer, treatment of acne and alopecia. But they may increase risk of venous thromboembolism, strokes, heart attacks mainly in older, smoking women with preexisting medical problems, such as diabetes mellitus and hypertension. Modern lower-dose hormonal contraceptives do not increase the risk for breast cancer, cholelithiasis, fibroids, and heart attacks in healthy women.

The hormone patches release estrogen and progestin through the skin for 7 days. They are adhesive and attached to a non-hairy part of the skin. After three weeks of using patches, there is a 1 week break. During this week the menstrual bleeding occurs. Hormonal patches may cause visible irritations of the skin and cause possible breakthrough bleeding.

The hormone vaginal rings are placed into the vagina for 3 weeks. They give continuously contraceptive effect. On the first day of the fourth week, vaginal ring should be removed. During this week menstrual period starts.

Combined hormonal contraceptives have some side effects, such as unscheduled bleeding or spotting, breast tenderness. But these changes are transient and may occur during first three months of using.

Progestin-only contraceptives are available in pills and injections. Depo Provera is an injection of long-lasting synthetic progesterone, which prevents ovulation. The effect of this injection lasts for three months. In 99% of cases it is reliable, and only requires to be injected four times a year. Disadvantages of this injection are possible breakthrough bleeding

and weight gain. Contraindication for use of progestin-only methods is a history of a breast cancer in the past 5 years. Progestin-only contraceptives help to reduce incidence of menorrhagia, dysmenorrhea, and pain, caused by endometriosis, incidence of endometrial cancer, and acute sickle and crises.

The very low-maintenance hormonal method of contraception is hormonal implant. The etonogestrel containing system Implanon suppresses ovulation and thickens cervical mucus to block sperm entry. It is indicated for up to 3 years of use. Implanon is a plastic rod measures 4 cm in length and 2 mm in diameter, similar to a size of a matchstick. The rate at which etonogestrel is released is controlled by a releasing membrane that surrounds the rod. It is inserted beneath the skin of upper arm under local anesthetic in the office. Contraindication for implants use is history of breast cancer in last 5 years. Disadvantages of implants are irregular periods, which can alternate among amenorrhea, oligomenorrhea, unscheduled bleeding and spotting, regular menses, and also mood swings and breast tenderness.

Intrauterine contraceptives

Intrauterine contraceptives are small T-shaped devices. There are two types of intrauterine devices (IUD) are available: the copper and levonorgestrel-releasing intrauterine systems. The copper IUD remains effective for at least 30 years. It provides excellent pregnancy protection and rapidly reversible. The failure rate during first year of using is 0.7%. Many women prefer this method of contraception. The only contraindications for administration of copper IUD are active infection

of reproductive organs and cancer of the cervix or uterine cavity. The copper IUD immobilizes and kills the sperm by changing the chemical content of the cervical mucus. IUD is inserted by a doctor in the office for the period of 3-5 years. Women using this IUD should check their tail string monthly to verify that their device is still in place. Sometimes copper IUD may cause heavy periods and it not protects from STIs.

The levonorgestrel-containing system-Mirena is a newer, progesterone coated plastic device. The levonorgestrel is slowly released and deactivates the sperm, so they cannot travel into the fallopian tubes. The effect of LNG-IUD lasts for 5 years. Women generally experience frequent episodes of unscheduled bleeding or spotting usually 1-3 days in a month. LNG-IUD reduces incidence of heavy and painful periods, prevents hyperplastic processes of endometrium and ovaries, and has a therapeutic effect in treatment of endometriosis and uterine myomas. LNG-IUD is thought to be more than 99% effective in pregnancy preventing, but it is not effective in preventing of STIs. (Figure 14.1-3)

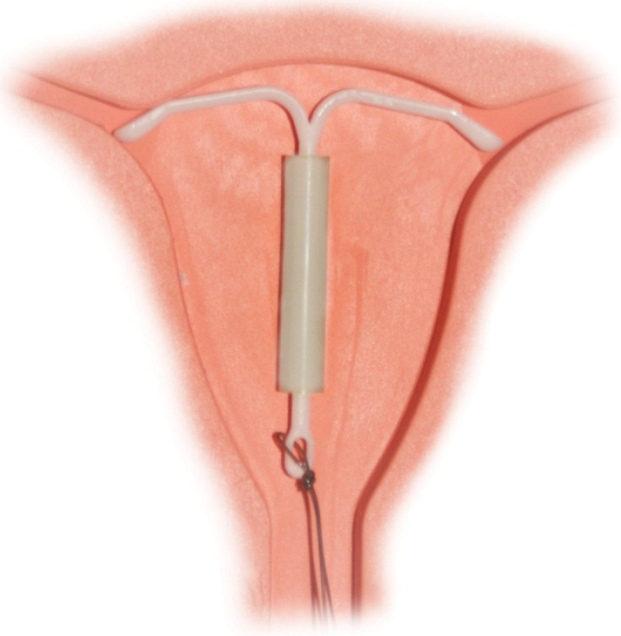


Figure 14.1-3 Hormonal intrauterine system “Mirena”

14.2 Sterilization

One of the methods of birth control is sterilization. It is permanent method of contraception, and leave person unable to reproduce. Sterilization methods are done for both males and females. There are surgical and non-surgical methods of sterilization.

Female sterilization is directed to prevent pregnancy. It works by blocking fallopian tubes. Sterilization is the good option for women, who don’t desire future fertility. Female sterilization is nearly 100% effective in preventing pregnancy. According to investigations, about 2-25 out of 1000 women might get pregnant after tubal ligation. According to a survey from Centres for Disease Control and Prevention, approximately 27% of American women of reproductive age use female sterilization as a method of birth control. This is equivalent to 10.2 million women. It was also find out, that black women are more likely to use female sterilization (37%), than white women (24%). Female sterilization is more popular among women of age group 40-44 years old.

The purpose of female sterilization is blocking sperm traveling into the fallopian tube. So, closure of the fallopian tube by surgical and non-surgical procedures is the mechanism of sterilization. But hysterectomy performed for other indications also sterilizes a woman. Surgical tubal

ligation prevents pregnancy immediately after the procedure, while nonsurgical sterilization may take up to three month to be effective.

The surgical procedure is tubal ligation, in which the fallopian tubes are cut or sealed. Tubal interruption can be done through a mini-laparotomy incision, a small subumbilical incision immediately postpartum, or during cesarean delivery, or using laparoscope. Laparoscopic approaches are more preferable, because of short operating time and hospitalization period, minimal blood loss, quick recovery period and minimal pain. Laparoscopic sterilization is usually performed as interval procedures in nonpregnant women when the woman's uterus lies in the pelvis. The fallopian tubes can be ligated with cautery, clips, or rings.

(Figur 14.2-1)

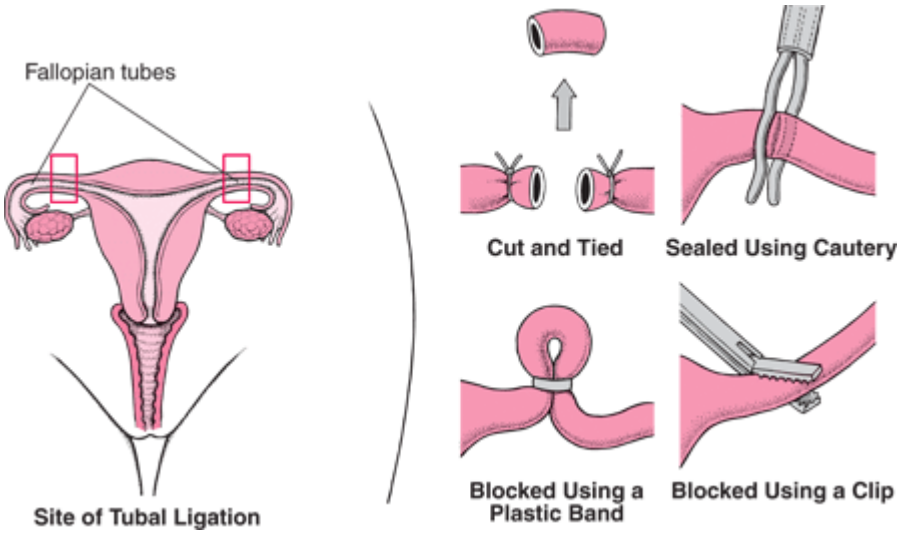


Figure 14.2-1 Methods of surgical tubal ligation

Nonsurgical procedures use devices placed in the fallopian tubes through the hysteroscope to seal them. Small plugs can be anchored in the proximal portion of the tube to incite fibrosis and, over time, cause the tubes to occlude. No incision is necessary, so recovery period is short. The procedure can be done in the office using local anesthesia or sedation.

Nonsurgical sterilization is less effective than surgical sterilization, especially in the first year. There was find out, that approximately 96 out of 1000 women got pregnant after this procedure.

Reversibility of sterilization procedures varies by technique and by amount of fallopian tube destroyed by initial procedure. Studies show that sterilization methods are less effective in younger women. The failure rate of posrpartum sterilization is the lowest, approximately 2%.

There is one-in –three chance that any pregnancy occurring after sterilization will be ectopic. It occurs when the fetus implants in the any part of occluded fallopian tube.

Male sterilization is vasectomy. It is permanent sterilization method; technically it is interruption of the vas deference. The procedure can be done in the office and may or may not require local anesthesia. There is no data available about long-term efficacy of vasectomy. A vasectomy typically takes between 2-4 months to become effective after procedure. But some studies show that azoospermia achieved following 6-10 ejaculations after the procedure. (Figure 14.2-2)

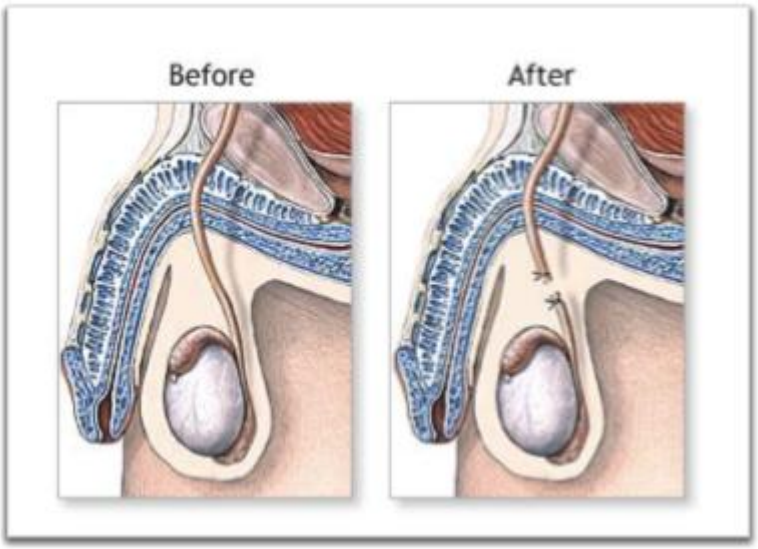


Figure 14.2-2 Male vasectomy

For some couples it is the optimal sterilization method because of safety and minimum if invasion and absence of risk for ectopic pregnancy. There are no hormonal, metabolic or functional effects associated with vasectomy. Vasectomy doesn't protect against STIs. That's why additional barrier methods of contraception are indicated.

14.3 Abortion

Abortion is termination of established pregnancy before the fetus is viable. The term abortion is commonly used for the induced, deliberated abortions, whereas the term miscarriage is usually used for spontaneous abortions.

It is estimated that 56 million induced abortions occurred each year worldwide. This number significantly increased within last 10 years, mainly because of population growth. Globally, 255 of pregnancies

ended in abortion. The highest rate of abortion was confirmed in Caribbean and the lowest in North America and Western and Northern Europe.

Although induced abortions are medically safe when done in accordance with recommended guidelines, many women undergo unsafe procedures that put their well-being at risk. Recent studies estimate that 8-18% of maternal deaths worldwide are due to unsafe abortion, and the number of abortion-related deaths in 2014 ranged from 22500 to 44000. The incidence of maternal death due to abortion is the highest in less developed countries. Maternal mortality rates decreases significantly in countries where abortion is legalized. Using of different methods of contraception decreases incidence of induced abortions. So, introduction and use of modern methods of contraception is an important strategy for reducing unintended pregnancies, abortions and unplanned births.

Every pregnant woman needs to be made aware of all her options, including continuing the pregnancy, abortion, and adoption. Decision in these areas are extremely difficult and personal because of variety of factors, such as marital, economic-social status of women, level of education, and legislation of different countries. In some countries abortion is prohibited by legislation.

There two types of induced abortion; medical and surgical. Which type of abortion to choose depends on age of gestation?

-abortions performed prior to 7 weeks of gestation are performed either surgically or medically (with drugs)

-from 7 weeks until 14 weeks, an abortion is performed by dilatation and suction curettage procedure

-after 14 weeks, surgical abortions can be performed by a dilatation and evacuation procedure

-after 20 weeks of gestation, abortions can be performed by labor induction, prostaglandin labor induction, saline infusion, hysterectomy, or dilatation and extraction.

Most of abortions are performed as outpatient procedure under local or intravenous anesthesia or without any sedation.

Medical abortions are safe, because there is no risk for maternal injury. In September 2000, the FDA approved the drug mifepristone (RU-486) for use in a specific medical plan that includes giving another drug, misoprostol, for those who do not abort with mifepristone alone. The efficacy of this method is 96%. Mifepristone induces uterine contractions expelling the products of conception. The process of a medical abortion involves bleeding, often like a heavy menstrual period, which must be differentiated from hemorrhage.

Early surgical abortions are performed with a cannula attached to manual vacuum or suction machine after little cervical dilatation has been achieved with misoprostol or laminaria. Laminaria japonica is a small sterilized stick placed into cervix to open it. After adequate dilatation of the cervix aspiration of the products of conception performed manually or with suction machine. Complication rates are

very small, but complication as infection, hemorrhage, retained products of conception, and anesthetic are possible.

Second-trimester abortions are generally performed by medical indications, when prenatal diagnosis has revealed serious chromosomal, genetic or developmental abnormalities, intrauterine demise of the fetus, or serious maternal conditions interfere with pregnancy. Dilatation and evacuation is the safest and most common method of second-trimester abortions. Ultrasound may be used to guide the procedure. Intravenous anesthesia is required. Intravaginal suppositories of prostoglandin and mifepristone are used for dilatation of the cervix and induce of uterine contractions. Occasionally the uterus is emptied with a sharp metal curette. These curettes are more dangerous than the flexible or rigid plastic devices, which are used in the suction. This may cause trauma of the uterus and cervix during the procedure.

Although early abortions made by professional providers are safe, a variety of complications are possible. Infertility, infections, failure of menstrual function, trauma, inflammatory diseases of the reproductive organs and even maternal mortality are the most common complications of the abortions. So, prevention of unintended pregnancy by using modern contraceptive methods is preferable.

Chapter review

1. The incidence of abortion is the highest in the following age group:

A) 35-44 years old

B) Younger than 20 years old

C) 25-34 years old

D) 20-24 years old

E) 20-30 years old

2. Which of the natural methods of contraception is the most effective?

A) Withdrawal or coitus interraptus

B) Calendar method

C) Abstinence

D) Lactational amenorrhea

E) Pregnancy

3. Which of the following is the main disadvantage of the natural methods of contraception?

A) High rate of failure in preventing of pregnancy and STIs

B) Difficulties of use

C) Require additional methods of contraception

D) Influence of fertility

E) Influence on hormonal balance

4. What is the failure rate of male condoms?

A) 2%

B) 5%

C) 1%

D) 8%

E) 0%

5. How long is the Implanon contraceptive effect lasting?

A) 3 years

B) 1year

C) 6 months

D) 5years

E) 2years

6. The contraceptive mechanism of combined oral contraceptives is:

A) Block the luteinized hormone surge and thicken cervical mucus

B) Change chemical content of cervical mucus

C) Increase production of FSH and LH

D) Deactivate sperm activity

E) Suppress GnRH production

7. Which of the following is not advantage of the hormonal method?

A) Prevention of STIs

B) Reduction of PMS

C) Regulation of heavy periods

D) Decrease of a risk for endometrial cancer

E) Treatment of acne and alopecia

8. What is the tubal sterilization technique with lowest failure rate?

A) Postpartum partial salpingectomy

B) Mini laparotomy tubal ligation

C) Laparoscopic tubal clipping

D) Hysteroscopic tubal occlusion

E) Laparoscopic salpingectomy

9. The main disadvantage of male sterilization is:

A) Does not prevent from STIs

B) Has hormonal effect

C) Increase risk of prostate cancer

D) Leads to functional failure

E) Affects the metabolism

10. Who are not candidates for an IUD?

A) Women with STIs

B) Women who desire long-term reversible contraception

C) Women with thromboembolism

D) Women with breast cancer

E) Breastfeeding women

Chapter 15 Surgical Procedures

Gynecological procedures have tendency to become minimally invasive and safer for last decades to improve lives of patients. Development of surgical techniques and equipment are resulting in more effective and efficient reproductive healthcare for women. At the present many gynecological surgeries require no incision or only a few tiny cuts. The general amount of these procedures is outpatient procedures. The introduction to the daily practice of smaller and more flexible instrumentation and development of robotic techniques are achievement of recent years.

Short recovery period, decreased hospitalization time, low risk for intra- and postoperative complications, low incidence of postoperative infection, minimal invasion and electivity are the main issues of modern gynecological procedures.

15.1 Abdominal and Vaginal Hysterectomy

The vast majority of gynecological surgery is done through the abdominal or vaginal incisions. The most commonly performed gynecological operation is hysterectomy. It is a surgical operation to remove the uterus. Although introduction and development of new conservative options in the treatment of gynecological diseases, incidence of hysterectomy is still very high and differ considerably

between countries. So, the highest rate of hysterectomy is in USA, approximately 5.4 per 1000 women, and the lowest in Norway-1.2 per 1000 women. The incidence rate has dropped by approximately 1% every decade since 1980; even so, almost 20% of women worldwide by age 55 years undergo hysterectomy.

There are a lot of conditions that may require hysterectomy. Most of them cause discomfort and inconvenience rather than threaten life. Usually these conditions have a great influence on a women's quality of life, affecting aspects of their daily routine, general health and sense of wellbeing. The general indications for hysterectomy are listed in the Table 15.1-1.

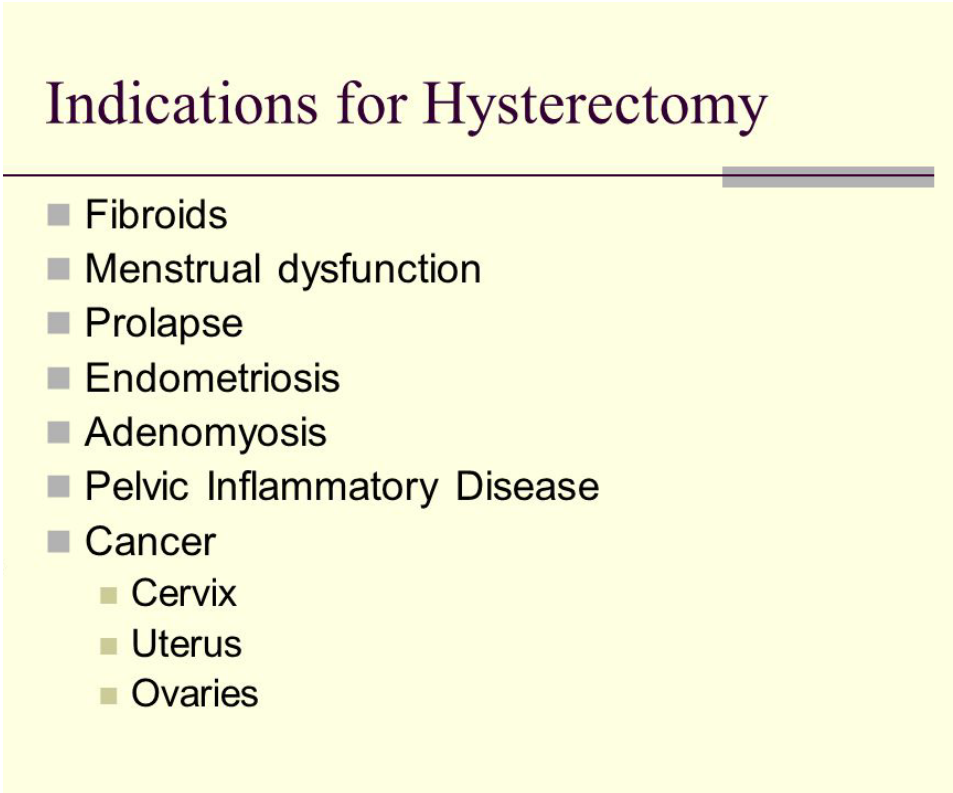


Table 15.1-1 General indications for hysterectomy

The most common indication for hysterectomy in pre-menopausal women is menorrhagia due to endometrial hyperplasia, uterine fibroids, or adenomyosis. Another common indication for hysterectomy is pelvic pain, mainly cause by endometriosis or adenomyosis. In these cases hysterectomy is treatment of choice for women with no intention of preserving fertility. Malignancy and postpartum hemorrhage are less frequent indications and account for only 10% of the total rate of hysterectomies.

Hysterectomy may be performed abdominally or vaginally.

Abdominal hysterectomy is the leading gynecological procedure for benign uterine conditions, and involves excision of the uterine corpus and cervix. Abdominal hysterectomy is divided on radical and subtotal. A radical hysterectomy involves the wide excision of the parametral tissue laterally, along with the uterosacral ligaments posterioirly. A subtotal hysterectomy involves the excision of the uterine corpus at the level of the internal cervical os. In menopausal women hysterectomy is usually following by removing of the adnexa. In premenopausal women the ovaries are recommended to preserve unless there is a strong family history of ovarian or breast cancer.

Abdominal incision may be transversal or vertical. The advantages of the transversal incision are better cosmetic result and low incidence of postoperative hernias. General anesthesia is required. (Figure 15.1-1)

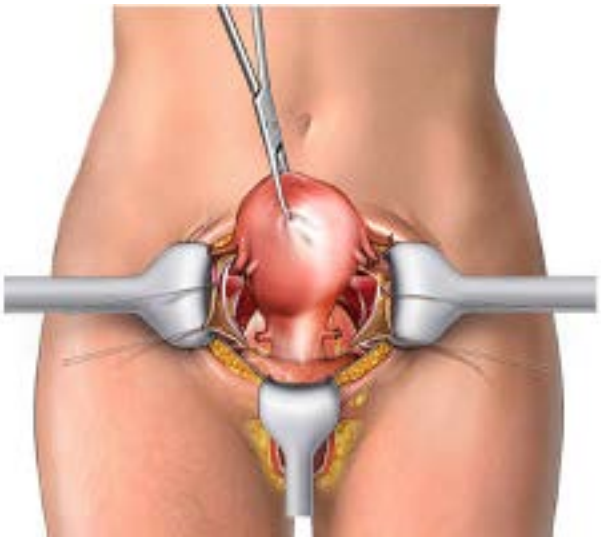


Figure 15.1-1 Illustration of abdominal hysterectomy, low transversal incision

After making an incision of the anterior abdominal wall and enter into the peritoneal cavity, the upper abdomen and intestines are manually explored. Then the patient is placed in the Trendelenburg position, and the abdominal viscera are packed out of the pelvis with laparotomy tapes.

Round ligaments are clamped, incised and ligated. The peritoneum on both sides is incised lateral to the infundibulopelvic ligament. This allows exposing the ureter and pelvic vessels. Then transversal incision of the vesicouterine fold between incised round ligaments is done. The bladder is reflected inferiorly off the fascia of the lower uterine segment, cervix, and the vagina. In case of adnexa removal the infundibulopelvic ligaments with the ovarian vessels are clamped, cut, and tied. If the adnexa are to be preserved, the ovarian ligaments are clamped, incised, and ligated on each side.

The uterine vessels are clamped at the level of internal cervical os, incised and ligated bilaterally. The ligated uterine vessels are reflected laterally, allowing access to the cardinal ligaments. Then cardinal ligaments are clamped, incised, and ligated medial to the uterine vessels. It may take several bites to free the cardinal ligaments from the lower cervix and upper vagina.

Posteriorly, the uterosacral ligaments are clamped, incised and ligated. The peritoneum is transversally incised between the uterosacral ligaments and the sides of the uterus reflected from the posterior surface of the cervix. So, the uterosacral ligaments are freed from the cervix and upper vagina. The total uterus is removed by cutting across the vagina just below the cervix. The vaginal cuff is closed with absorbable sutures, incorporating the cardinal and uterosacral ligaments into each lateral angle of the vagina to preclude the later development of a vaginal vault prolapse. Progressive circular sutures may be placed to obliterate a large pouch of Douglas to avoid the risk for enterocele.

After removing of tapes the abdominal cavity and abdominal wall are gradually closed by suturing.

Abdominal hysterectomy poses some risks of major and minor complications. Major medical complications after abdominal hysterectomy are: heavy blood loss, bowel and bladder injury, ureters injury, pulmonary embolism, anesthesia problems. Minor complications after abdominal hysterectomy involve: postoperative infection, hematoma of the surgery site, fever. Injury of the ureter is

the most serious complication of the hysterectomy. Use of retroperitoneal approach, with identification of the ureters bilaterally and careful reflection of the bladder inferiorly, prevents ureteric injury.

Late complications of the hysterectomy include:

-difficult urination, usually after radical hysterectomy

-weakness of the pelvic muscles, which results in the pelvic organs prolapse

-continued bleeding. Some vaginal bleeding within 4-6 weeks following a hysterectomy is expected

-early menopause

-the formation of the adhesions in the pelvic area

-dyspareunia

Recovering from a hysterectomy takes time. Usually it requires up to 5 days stay in the hospital. During 2 to 3 weeks, it is important to get plenty of rest. Complete recovery usually takes 4 to 8 weeks.

Vaginal hysterectomy is a type of hysterectomy, which is done through a small incision in the vagina. It is preferable to the abdominal approach and associated with less pain, affords an opportunity to correct pelvic relaxation, requires less postoperative hospitalization and disability, and leaves no scar. First vaginal hysterectomy was performed in 1813 by Langenbeck.

A vaginal hysterectomy can be performed by the following indications:

-small uterine fibroids

-normal or slightly enlarged size of the mobile uterus, less than 12 weeks of gestation

-absence of endometriosis implants

-absence of pelvic adhesions due to PID, or previous abdominal operations

-uterine prolapse, cystocele, rectocele, or enterocele in postmenopausal women

Vaginal hysterectomy requires more specialized surgical skill than abdominal hysterectomy, because of higher risk of injury of surrounding structures. Laparoscopically assisted vaginal hysterectomy has greatly expanded the indications for vaginal hysterectomy. Vaginal hysterectomy is not used when possible cancer of the uterus, cervix, or ovaries is a concern.

Vaginal hysterectomy requires dorsolithotomy position of the patient. The bladder is emptied, and a thorough pelvic examination is performed. The way in which the incision of the vaginal wall should be performed depends entirely on the individual anatomical conditions. Usually a transverse incision is made through the vaginal epithelium between the uterosacral ligaments at the posterior junction of the cervix and vagina. The blunt mobilization of the posterior peritoneum is performed. Finger exploration of the cul-de-sac and

posterior vaginal wall is done. Then uterosacral ligaments are clamped, cut, and ligated, which give possibility for the uterus to descent. (Figure 15.1-2)

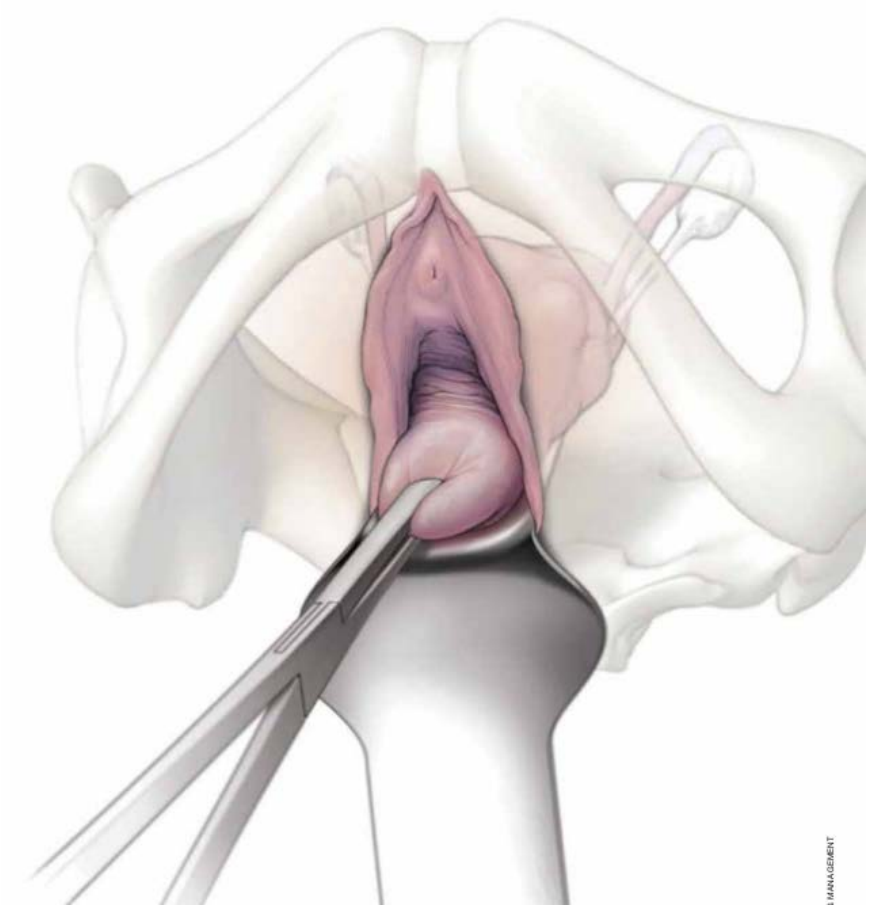


Figure 15.1-2 Vaginal hysterectomy

Next step is circular incision of the vaginal epithelium around the cervix. The bladder is advanced superiorly along the anterior uterine wall, exposing the anterior uterovesical fold of the peritoneum, which is sharply entered. The pubocervical ligaments containing the ureters are bluntly displaced laterally and the cardinal ligament are clamped, cut, and ligated, allowing further descent of the uterus. The bladder is retracted anteriorly by the angle retractor, which is placed into the

opening of the anterior vesicouterine fold. The uterine vessels are clamped, cut, and ligated. It is necessary to be ensured that all the uterine vessels are correctly clamped.

Downward traction of the uterus allows to clamping and ligating together as a group the round ligament, fallopian tube, ovarian ligament, utero-ovarian anastomose in each side of the uterus. It is necessary to perform double ligation of these structures. If the adnexa are to be removed, the suspensory ligament of the ovary is addressed instead of the ovarian ligament. A Heaney clamp is placed across the infundibulopelvic ligament, and the ovary and tube are excised.

Then a sponge-stick or laparotomy pad is placed into the peritoneal cavity to allow the surgeon to visualize each of the pedicles and confirm that hemostasis is adequate. If any bleeding points are identified, a suture is used to ligate the bleeding vessels under direct vision. The peritoneum is closed with several U-sutures, leaving the pedicles in an extraperitoneal position. To avoid further enterocele, uterosacral ligaments may be plicated by several sutures. The cardinal ligaments should be sutured to the lateral aspects of the vaginal cuff to provide vaginal support.

Finally, the vaginal epithelium is reapproximated either vertically or horizontally with either a continuous suture or a series of interrupted sutures. These sutures are placed through the full thickness of the vaginal epithelium, with care taken to ensure that the bladder is not entered.

There are very few absolute contraindications for vaginal hysterectomy, such as pregnancy, cancer, enlarged uterus, nulliparity, narrow pubic arch, and immobile uterus.

Different studies show that vaginal hysterectomy has better outcomes and fewer complications. The advantages of vaginal hysterectomy are shorter duration of hospital stay, faster return to normal activity, and low incidence of febrile episodes or unspecified infections.

The primary intraoperative complications of the vaginal hysterectomy are visceral injury (0.88-1.76%) and hemorrhage (1.4-2.6%). The most common postoperative complication is pelvic infection (4%).

15.2 Hysteroscopy

Gynecologic endoscopy has been progressively improved during last decades, and has largely moved from operating room to the freestanding outpatient unit. Refinements in optic and fiberoptic technology and inventions of new surgical accessories have dramatically improved visual resolution and surgical techniques of endoscopic procedures. One of the options of gynecologic endoscopy is hysteroscopy.

Hysteroscopy is a form of minimally invasive surgery. It is a process of observation and operating in the endometrial cavity from a

transcervical approach. Hysteroscopy can be used for to diagnose and treat many intrauterine and endocervical problems.

The development of hysteroscopy takes beginning from 1869s, from the work of Pantaleoni, who first reported uterine endoscopy. Initially used by urologists for transurethral resection of the prostate, the resectoscope was modified for hysteroscopic procedures. By the mid-1980s hysteroscopic procedures had nearly replaced dilatation and curettage for diagnosing intrauterine pathology.

The basic hysteroscope is a long, narrow telescope connected to a light source to illuminate the area to be visualized. The distal end of the telescope is passed into a dilated cervical canal, and, under direct visualization, the instrument is advanced into the uterine cavity. Two different types of telescopes are used today: rigid and flexible fiberoptic. Rigid telescopes are most commonly 1 to 5 mm in diameter for diagnostic procedures, and operative hysteroscopes typically range from 8 to 10 mm in diameter and contain a working element through which operative instruments, such as rigid of flexible scisors, graspers, biopsy forceps, and laser fibers are inserted. The telescopes consist of 3 parts: the eyepiece, the barrel, and the objective lens.

A camera is commonly attached to the proximal end of the hysteroscope to broadcast the image onto a large video screen. Other common modifications are inflow and outflow tracts included in the shaft of the telescope fluids. As uterine cavity needs distention for adequate visualization, media, such as sodium chloride solution or

carbon dioxide gas, can be pumped through a hysteroscope into the endometrial cavity. It is critically important for the surgeon to know which media are compatible with electrosurgical or laser energy sources and which are prone to fluid overload or anaphylactic shock during the procedure. (Figure 15.2-1)

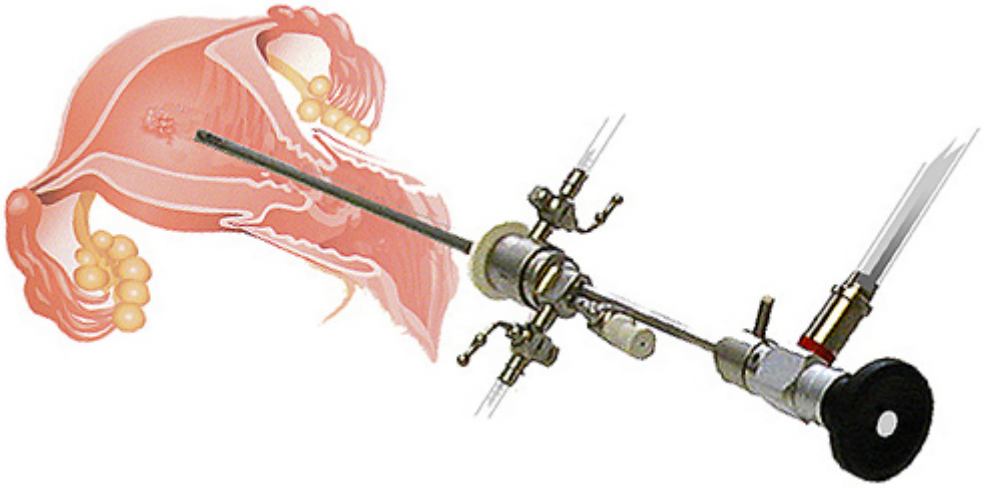


Figure 15.2-1 Procedure of Hysteroscopy

Monopolar and bipolar electricity, as well as laser energy, all have uses in hysteroscopy.

The most common indications for hysteroscopy are:

1. Abnormal uterine bleeding
2. Infertility
3. Intrauterine adhesions
4. Mullerian anomalies
5. Polyps and fibroids
6. Sterilization
7. Proximal tubal obstruction

Excessive blood loss is a strong indication for exploring the uterine cavity and determining the underlying pathology. Hysteroscopy had replaced D&C (dilatation and curettage) in diagnosis of untrauterine pathology. The failure rate of D&C in diagnosis is 10 -25%. Hysteroscopy with an endometrial biopsy is the procedure of choice in patients with abnormal uterine bleeding. Biopsy is especially important if hyperplasia, polyps, and endometrial cancer are suspected. Small endometrial polyps can be removed easily using hysteroscopic scissors or grasping forceps inserted through an accessory channel of the operating hysteroscope, or they can be removed blindly with a polyp forceps followed by hysteroscopic reinspection to ensure complete removal. Large polyps and myomas should be marcellated before removal. The urologic resectoscope has been used to marcellating or vaporization all or part of these lesions. (Figure 15.2-2)

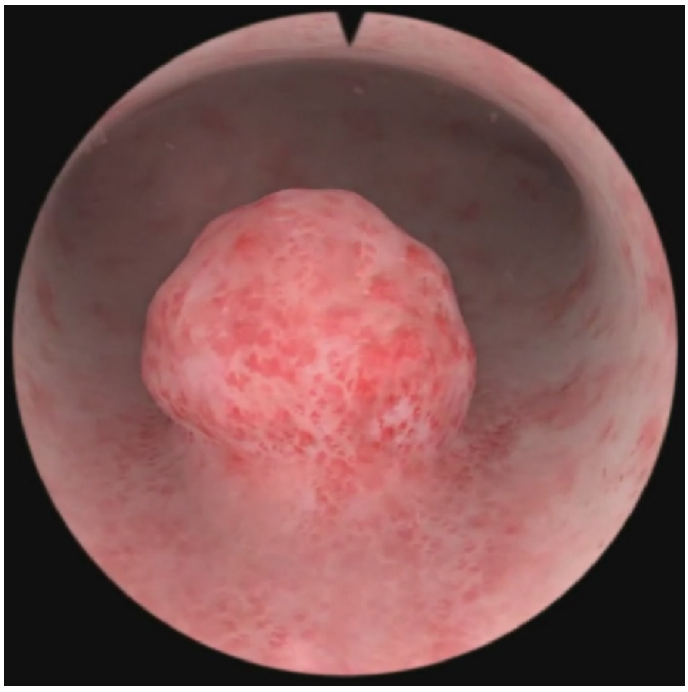


Figure 15.2-2 Hysteroscopic view of the endometrial polyp

Hysteroscopy can provide valuable information in diagnosis of endometrial hyperplasia and neoplastic lesions of the endometrium. Hysteroscopy has the advantage of permitting a targeted biopsy in the event of localized lesions, and permits proper classification of the extent and degree of hyperplasia.

Despite well established techniques, in the investigation of infertility, only hysteroscopy permits an accurate assessment of the genital tract in infertile women. One of causes of infertility and amenorrhea are intrauterine adhesions. Hysteroscopy aids both the diagnosis and management of intrauterine adhesions. It allows a panoramic as well as a close view with x20 magnification. Endometrial adhesions are usually fragile, soft, and whitish in appearance and are easily divided. Developed as a result of trauma, such as curettage or other uterine surgery, adhesions may vary from mild to severe, obliterating only a small part or almost all the endometrial cavity. Hysteroscopic scissors, laser, or knife electrodes are most commonly used for incision of the adhesions. Successful management can be achieved in many cases, resulting in normal menstrual flow in 86.7% and pregnancy rate of 44%.

Hysteroscopy is also recommended for the diagnosis and treatment of congenital uterine abnormalities, to assess the anatomical and functional condition of the uterotubal ostia, to determine and guide postsurgical management of metroplasty and salpingoplasty, to identify and assess the uterine cavity in cases of recurrent abortions.

The excision of the intrauterine septum, a congenital anomaly that occurs in up to 1% of women, is one of the most rewarding hysteroscopic procedures.

Ablation of the endometrium is one of the treatment options of hysteroscopy. Two general methods of endometrial ablation are performed. The first type requires hysteroscopic visualization and employs electrical or laser energy to shave, vaporize, or coagulate the endometrial surface. Resectoscopic ablation is the most popular technique of endometrial ablation. Incidence of amenorrhea after resectoscopic ablation is up to 70%, whereas incidence of hypomenorrhea is more than 90%. Second method of endometrial ablation does not require hysteroscopic visualization, and based on the delivery of heat to the endometrial surface or microwave energy directed at the endometrium.

Diagnostic hysteroscopy is a safe procedure. Complications mainly occur when inappropriate instruments or techniques are used. The overall complication rate is about 2%. The incidence of major complications, such as perforation of the uterus, hemorrhage, fluid overload, bowel or urinary tract infection is less than 1%. The most frequent complications of hysteroscopy are the result of over distention of the uterine cavity. Complications can also occur when using Dextran-70, and include pulmonary edema, anaphylactic reactions and coagulopathy consequent to intravasation. Uterine perforation is a rare event, and occurs in 4 out of 1000 cases of diagnostic hysteroscopy. Perforation usually occurs in difficult cases during dilatation of the cervix. Incidence of infection after

hysteroscopy is very low, approximately 02% in over 4000 diagnostic hysteroscopies.

5.3 Laparoscopy

Laparoscopy is a type of endoscopic surgical procedure that allows a surgeon to access the abdominal and pelvic cavity without having to make large incision in the skin. It is a kind of minimally invasive surgery with using of laparoscope. Laparoscope is an instrument for viewing the peritoneal cavity. This is a small tube that has a light source and attached camera, which allows reflection of the images of the inside of the peritoneal cavity to a television monitor. Multiple small puncture sites through the skin and into the abdominal cavity are used for insertion of narrow rigid or flexible instruments toward the peritoneal cavity. (Figure 15.3-1)

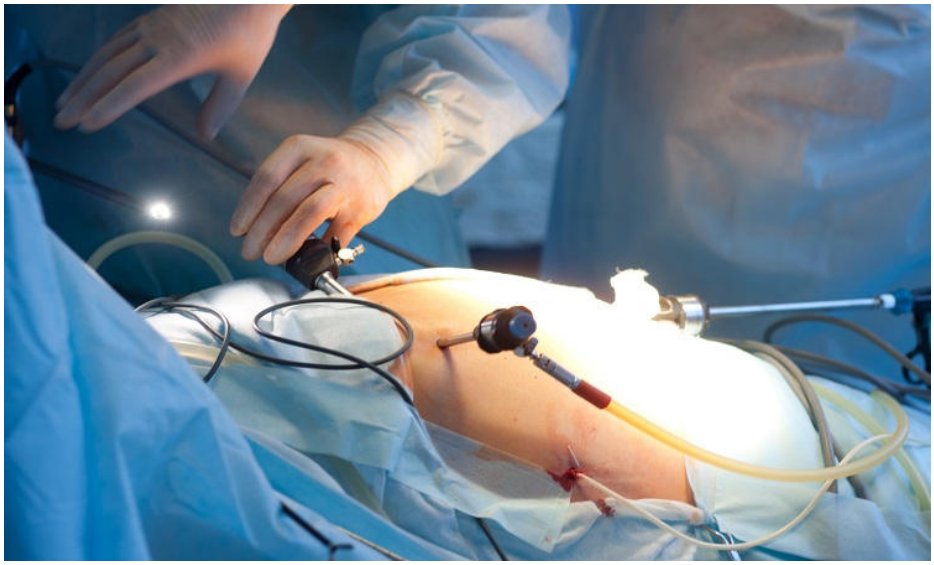


Figure 15.3-1 Laparoscopy

The advantages of laparoscopic technique over traditional open surgery include:

-a shorter hospital stay and faster recovery time

-low incidence of intra- and postoperative hemorrhage

-reduced scarring

During 40 years, laparoscopy has envolved from a limited gynecologic surgical procedure used only for diagnosis and tubal ligation to a major surgical tool used for a multitude of gynecologic and nongynecologic indications. Laparoscopy was first performed in dogs in the early 1900s by Dr.George Kelling, a German surgeon, who called his procedure koelioskopie. Early in the 20^{th} century, diagnostic laparoscopy was used by a limited number of general surgions in place of diagnostic laparotomy, but had a substantial complication rate. Dr. Raoul Palmer, a French gynecologist who specialized on infertility, was an early pioneer in the development of gynecological laparoscopy. Today, operative laparoscopy is a routinely used by gynecologist to perform a multitude of procedures, including hysterectomies and incontinence procedures, and for diagnosis and treatment of even gynecologic malignancies.

Modern laparoscopy introduces a lot of innovations, including robotic surgery, single port laparoscopic surgery, and using of laser technologies.

Laparoscopy is a hybrid surgical approach that shares characteristics of both minor and major surgery. Usually, a primary port for the laparoscope is placed infraumbilically and a second port is placed suprapubically to probe systematically and observe pelvic organs. Despite, laparoscopy is an intraabdominal procedure; it shares all intra- and postoperative risks of laparotomy. Laparoscopic procedures have unique risks, which are related to methods used for the placement of abdominal wall ports and to the pneumoperitoneum required for laparoscopy. The use of energy within the abdominal cavity also introduces risk. The patients should be carefully assessed on presence of the following risk factors before the procedure:

-obesity, which increases the risk of any abdominal surgery

-age; high incidence of intra- and postoperative complications in older patients

-previous abdominal surgery, for the high risk of intraabdominal adhesions

Diagnostic laparoscopy is usually requires general anesthesia, with endotracheal intubation to minimize the risk of aspiration. There is a wide specter of indications for laparoscopy, including both diagnostic and therapeutic indications. The most common indication for the use of the laparoscope in gynecology is sterilization. Bipolar electrosurgery, clips, or silastic bands may be used to occlude the tubes.

Laparoscopy is a treatment of choice for most ectopic pregnancies. A salpingostomy or salpingectomy may be performed to remove the embryo and gestational sac.

Both diagnostic and therapeutic laparoscopic procedures are included to the standard algorithm of evaluation and treatment of infertile patients. Advanced assisted technologies require laparoscopic procedures as well.

Laparoscopy is the most common procedure used to diagnose and treatment of endometriosis. It is widely used for resection, ablation or vaporization of endometriosis heterotopies by using of different power instruments. Laparoscopic procedures for endometriosis have very good outcomes, such as improved fertility and decreased pelvic pain.

Lysis of adhesions is one of the most common indications for laparoscopy. Adhesions may form due to prior infections, endometriosis, or pelvic surgery. They are main contributors to female infertility. Adhesions may be lysed by blunt or sharp dissection, or by using of any of power instruments. Unfortunately, adhesions may reform after lysis, and it is disappointing in terms of improving pain relief or future fertility. It is also often ineffective in curing of chronic pelvic pain. But acute and chronic pelvic pain can be investigated using the laparoscope.

Laparoscope can be used as a less invasive procedure to evaluate adnexal mass. Benign and malignant ovarian neoplasms can be managed by laparoscope. If a simple ovarian cyst sized 6 cm or larger

persist for 2 or more cycles in premenopausal women, a laparoscopic cystectomy is indicated. Laparoscopic aspiration of cysts can be dangerous and may result in dissemination of an unsuspected ovarian cancer. The cysts can be removed by a number of techniques. If malignancy is found, a laparotomy should be performed.

An oophorectomy may be more appropriate in postmenopausal women with growing or persistent ovarian cyst. The power instruments, prettied loops, or stapling devices may be used to occlude the infundibular ligament and safely remove the ovary.

Laparoscopic myomectomy has become more popular. Many patients prefer myomectomy to hysterectomy in order to preserve the uterus. There is recommendation for laparoscopy can be used for removing of fibroids not larger 6 cm. The most common indications for laparoscopic myomectomy are pedunculated fibroids. For intramural fibroids the risk of bleeding increases. An injection of vasopressin into the uterus may help maintain hemostasis. The fibroids may be removed by marcellation or colpotomy. Some studies show that the risk of subsequent uterine rupture during pregnancy may be greater after laparoscopic myomectomy compared with laparotomy.

Laparoscopy is widely used to perform hysterectomy, especially those assisted with a vaginal hysterectomy. The three basic laparoscopic approaches for hysterectomy are laparoscopic-assisted vaginal hysterectomy, laparoscopic hysterectomy, and laparoscopic supracervical hysterectomy. Each of these techniques has its risks and benefits. (Figure 15.3-2)

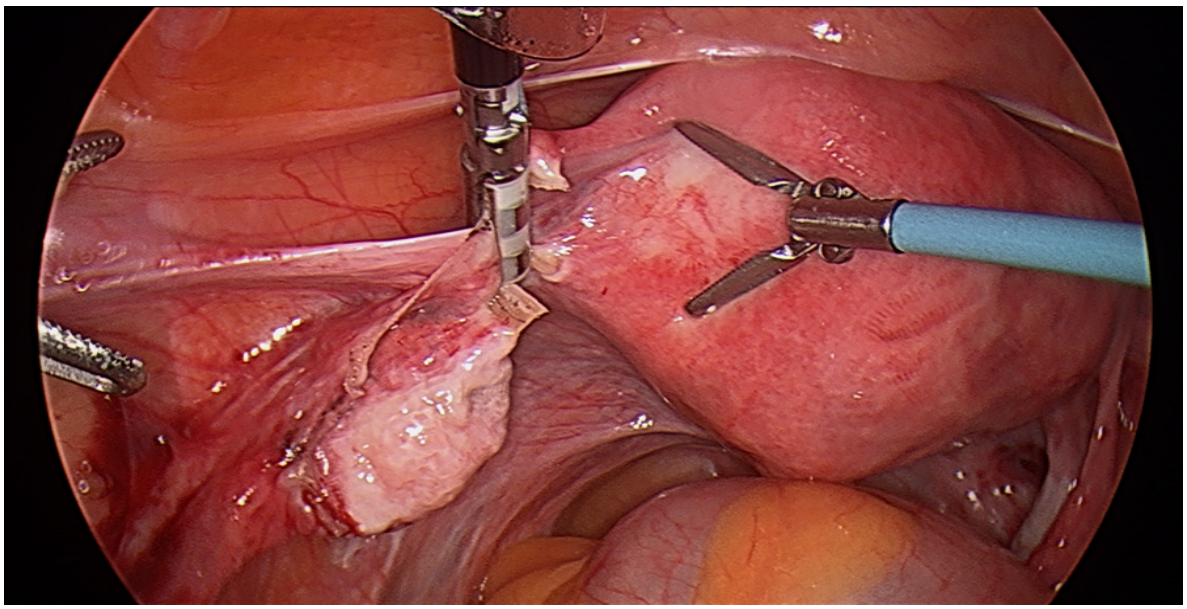


Figure 15.3-2 Laparoscopic hysterectomy

The procedure of laparoscopy is performed with the patient in a modified dorsal lithotomy position. A pneumoperitoneum is created by inserting of a spring-loaded needle, into the peritoneal cavity through the subumbilical fold, and insufflation with CO2 or nitrous oxide. The trocar and surrounding sheath are then inserted through a small subumbilical incision. The lighted telescope is inserted into a sheath and advanced slowly. When the visualization of pelvic organs confirms that the peritoneal cavity has been entered, gas is added to maintain a sufficient pneumoperitoneum. The trocar and operating instruments are inserted through the small punctures, which performed into the abdominal with the control of camera to avoid injury of the inferior epigastric vessels.

The operation is finished by checking of hemostasis, releasing of the gas from the peritoneal cavity and withdrawal of instruments. Small skin incisions are closed by suturing.

There are no absolute contraindications for gynecologic laparoscopy. The most common suggested contraindications are pregnancy, ongoing gynecologic malignancy, and hemodynamic instability, resulting from a ruptured ectopic pregnancy.

Major laparoscopic procedures are associated with a higher rate of complications compared with minor procedures, 06% to 18% and 0.06% to 7.0% respectively.

The majority of complications occur during entry of instruments into the abdominal cavity used to create pneumoperitoneum. Other causes for complications are thermal and energy source injuries, operative manipulations, and presence of CO2 out of the peritoneum. The incidence of bowel injury is reported to be 0-0.5%, and considered the most serious complication of laparoscopy. Bowel burns either from direct contact or from a unipolar spark are usually not detected at the time of the procedure. In several days bowel perforation with further peritonitis may be evident. The injuries of the urinary tract organs and abdominal wall vessels are other most common complications of the laparoscopy. The incidence of abdominal wall bleeding is 0.3 to 0.5%. Of all urinary injuries, 64.7% occurred with laparoscopic-assisted vaginal hysterectomy, 18.0% during operations on endometriosis, and 12.3% during diagnostic or sterilization procedures. Among the delayed complications of the laparoscopy the

most common is a formation of the hernia, with incidence of 0.17% to 0.2%. There is also an increased risk for intraoperative anesthetic complications in patients with a pneumoperitoneum. Hypercarbia and therefore acidosis develop due to absorption of CO2 in prolonged operations.

Chapter Review

1. What is the annual incidence of hysterectomy in women of age group by 55 years old?

A) 20%

B) 30%

C) 10%

D) 50%

E) 15%

2. Which of the following is not indication for abdominal hysterectomy?

A) Pedunculated small polyp of the endometrium

B) Uterine myoma

C) Complex endometrial hyperplasia with atypia

D) Adenomyosis

E) Pregnancy catastrophe

3. The uterine arteries are clamped and cut on the level of:

A) Internal cervical os

B) Midpoint of the cervix

C) External cervical os

D) Lower uterine segment

E) Upper third of the vagina

4. The following is not delayed complication of the abdominal hysterectomy:

A) Bowel and bladder injury

B) continuing vaginal bleeding

C) Difficulties of urination

D) Early menopause

E) Weakness of the pelvic muscles

5. Which of the following is not indication for vaginal hysterectomy?

A) Uterine fibroids larger than 12 weeks of gestation

B) Small uterine fibroids

C) Absence of endometriosis heterotopies

D) Uterine prolapse

E) Absence of pelvic adhesions

6. Hysteroscopy is:

A) A process of observation of the endometrial cavity through a transcervical approach

B) Dilatation of the cervical canal

C) Administration of a contrast dye into the endometrial cavity

D) Ablation of the endometrium

E) Observation of the endometrial cavity through the incision into the abdominal wall

7. The most common indication for hysteroscopy is:

A) Abnormal uterine bleeding

B) Intramural myoma

C) Adenomyosis

D) External genital endometriosis

E) Ectopic pregnancy

8. What is the overall complication rate of hysteroscopy?

A) 2%

B) 10%

C) 6%

D) 25%

E) 12%

9. Which vessels may be damaged during laparoscopy most of all?

A) Inferior epigastric vessel

B) Internal iliac artery

C) Uterine artery

D) Obturator vessels

E) External iliac vessels

10. Which fibroids are preferable to be removed by laparoscopy?

A) Pedunculated subserosal fibroids

B) Intramural fibroids

C) Submucosal fibroids

D) Intraligamentary fibroids

E) Large subserosal fibroids

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