MINISTRY OF HEALTH OF UKRAINE
ODESSA NATIONAL MEDICAL UNIVERSITY

Faculty of international

Department of Obstetrics and Gynecology

APPROVED
Vice-rector for scientific and pedagogical work
Eduard BURIACHKIVSKYI
"29" August 2024

METHODICAL DEVELOPMENT
to the lecture

Course IV Faculty international

Discipline Obstetrics and gynecology

LECTURE №2 TOPIC. Benign tumors of female genital organs. Precancerous diseases of female genital organs.

Approved:
Meeting of the Department of Obstetrics and Gynecology of Odesa National Medical University

Protocol №1 dated August 29, 2024.

Head of the department _____ (Ihor GLADCHUK)

Developer: associate professor of the department of Obstetrics and Gynecology _____ Kozhakov V.L.

TOPIC. Benign tumors of female genital organs. Precancerous diseases of female genital organs.

1. **Importance and background of the topic.** The problem of benign and precancerous diseases of female genital organs is significant all over the world. Mainly it is due to the high frequency of these diseases, their potential to malignization, disabling of reproductive function and invalidization of patients. Majority of gynecological operations including hysterectomy have indications of benign and precancerous process of female genitals. It creates not only social but also economical burden of these diseases.

2. Aims of the lecture:

- ***educational:*** to introduce students to main benign and precancerous diseases of female genital organs, to teach methods of diagnostics and differential diagnostics, prevention and treatment of these pathologies.
- ***formative:*** formation of contemporary professional thinking in students; stressing of the role of different and local scientific schools in research of this problem; learning of deontological and ethical aspects. Learn to make plan of examination, including necessary invasive methods. Carry out modern methods of examination which allow to find and include all specifics that enable correct diagnostics and determination of further management.

Ovarian tumors

Summary

The ovaries consist of different kinds of tissue (epithelial, germ cells, and sex cord tissue), which may give rise to benign or malignant tumors. Symptoms depend on the type of tissue affected and range from local abdominal discomfort to endocrinological phenomena caused by hormone-producing tumors.

Ovarian cysts

Ovarian cysts are fluid-filled sacs within the ovary. The most common types are functional follicular cysts, corpus luteum cysts, and theca lutein cysts, which all develop as part of the menstrual cycle and are usually harmless and resolve on their own. Nonfunctional cysts include chocolate cysts, which are related to endometriosis, dermoid cysts, cystadenomas, and malignant cysts (a type of ovarian cancer). All types can be diagnosed via pelvic ultrasound. While ovarian cysts are usually asymptomatic, complications due to rupture of a cyst can occur and may require treatment. Moreover, individuals with ovarian cysts are at increased risk of ovarian torsion, which requires surgical correction.

Definition

Ovarian cysts are fluid-filled sacs within the ovary.

Types

- **Functional cysts**: result from a disruption in the development of follicles or the corpus luteum; often resolve on their own
- **Follicular cyst of the ovary** (most common ovarian mass in young women)
- Develops when a Graafian follicle does not rupture and release the egg (ovulation) but continues to grow; eventually becomes a large cyst (7 cm) lined with granulosa cells
- Associated with hyperestrogenism and endometrial hyperplasia
- **Corpus luteum cyst**
- Enlargement and buildup of fluid in the corpus luteum after failed regression following the release of an ovum
- Produces progesterone, which may delay menses
- Associated with progesterone-only contraceptive pills and ovulation-inducing medication

- **Theca lutein cysts**
- Multiple cysts that typically develop bilaterally
- Result from exaggerated stimulation of the theca interna cells of the ovarian follicles due to excessive amounts of circulating gonadotropins such as β-hCG
- Strongly associated with gestational trophoblastic disease and multiple gestations
- Usually resolve once ß-hCG levels have normalized
- **Nonfunctional cysts**
- **Chocolate cysts**: related to endometriosis
- Dermoid cysts
- Cystadenoma (serous or mucinous)
- Malignant cysts (form of ovarian cancer): higher risk in postmenopausal women

Clinical features

- Most often asymptomatic unless complications occur
- In some cases, there may be signs of the underlying cause (e.g., menorrhagia in endometriosis or hirsutism, acne, and infertility in PCOS).

Diagnosis

- Pelvic ultrasound
- **Smooth** lining on all sides
- Single (e.g., follicular cyst of the ovary, corpus luteum cyst) or multiple (e.g., polycystic ovary syndrome, multilocular theca lutein cysts)
- Hypoechoic to anechoic
- Fluid level

Complications

- Ovarian torsion
- Ruptured ovarian cyst

Treatment

- In most patients with functional cysts, watchful waiting is recommended, as cysts often regress spontaneously.
- NSAIDs in the case of painful cysts
- Surgery in the case of complications, large cysts, or persistent cysts that are painful
- Treatment of underlying conditions such as PCOS, endometriosis, or ovarian cancer

Ruptured ovarian cyst

- **Etiology**: physical activity
- **Clinical features**
- Sudden-onset **unilateral** lower abdominal pain
- In the case of a very large cyst: Fluid and blood loss may cause acute abdomen and shock.
- **Diagnosis**: Pelvic ultrasound shows free fluid, most commonly in the pouch of Douglas (rectouterine pouch).
- **Treatment**
- Hemodynamically stable patients can be observed and given analgesics.
- Hemodynamically unstable patients require **laparoscopy** to control hemorrhaging.

Ovarian torsion

- **Etiology**
- Physical activity
- The primary risk factor is **ovarian enlargement** (e.g., due to cysts, ovarian stimulation, pregnancy, tumors).
- **Clinical features**
- **Sudden-onset** unilateral lower abdominal pain
- Nausea and vomiting
- **Diagnosis**: Pelvic ultrasound with Doppler velocimetry shows enlarged, edematous ovaries with decreased blood flow.
- **Treatment**: Detorsion via laparoscopic surgery is recommended as soon as possible to restore blood flow.

Ovarian tumors
Epidemiology

- Lifetime prevalence of malignant ovarian cancer: 1–2%
- Peak incidence: 60–70 years
- Genetic predisposition may play a role in familial incidence and in younger patients (< 30 years) developing tumors.
- Epithelial ovarian carcinomas account for 70% of all ovarian malignancies.

Etiology

Risk factors

- **Genetic predisposition**
- **BRCA1/BRCA2 mutation**
- **HNPCC syndrome**
- Peutz-Jeghers syndrome
- **Hormonal imbalance and menstrual cycle**
- Elevated number of lifetime ovulations (the contraceptive pill appears to have a protective effect)
- Infertility/low number of pregnancies
- Early menarche and late menopause
- PCOS

Overview of ovarian tumors

Epithelial Tumors

- 65–75% of all ovarian tumors; ~ 70% of all malignant ovarian tumors
- **Cystadenoma/cystadenocarcinoma**
- **Serous**
- Most common ovarian tumor
- Serous cystadenocarcinoma is the most aggressive ovarian cancer
- Frequently bilateral (65% of cases)
- Histology:
- Tumor cells with papillary structures and small cytoplasm
- **Psammoma bodies** are a typical feature.
- **Mucinous**
- Second most common ovarian tumor
- Up to 75% of cases are benign.
- **Endometrioid carcinoma**
- Frequently associated with endometrial cancer and endometriosis
- Commonly malignant
- Clear cell carcinoma

Epithelial ovarian tumors may be benign, malignant, or borderline!

Germ cell tumors

- 15–25% of all ovarian tumors
- **Teratoma**
- **Mature**
- **Dermoid cysts**: most common of all germ cell tumors (90% of cases)
- Malignant transformation in 2% of cases
- Can theoretically contain any type of tissue, e.g., hair, teeth, and sebaceous glands, but mostly include parts of ectodermal origin
- Differentiated, mostly benign tumor
- **Struma ovarii**: teratoma with endodermal differentiation into thyroid tissue
- Very rare: malignant transformation into a thyroid carcinoma
- May produce thyroxine and cause hyperthyroidism symptoms
- Differentiated, mostly benign tumor
- **Immature**:
- Rare, undifferentiated
- May contain tissue of embryonic/fetal period
- High risk of malignancy
- **Dysgerminoma**: most common malignant ovarian tumor in young women (20–30 years); female histological equivalent to the male seminoma
- **Yolk sac tumor of the ovary**: often malignant; occurs mainly in childhood and adolescence
- **Non-gestational choriocarcinoma**: rare and extremely malignant; normally accompanied by beta hCG production

Sex cord-stromal tumors of the ovary

- 5–10% of all ovarian tumors
- Estrogen producing: **granulosa cell tumor** and **theca cell tumor**
- ~ 75% of cases affect postmenopausal women.
- Androgen producing: Sertoli-Leydig cell tumor
- Occurs very rarely; ~ 20% malignant transformation
- Production of androgens → virilization
- Primarily affects women aged 30–40 years
- Ovarian fibroma
- Benign, although may cause Meigs' syndrome

Metastasis

- 10–15% of all ovarian tumors
- Primary tumors are most often found in the gastrointestinal tract, breast, or endometrial cancer
- **Krukenberg tumor**: bilateral ovarian metastases from an undifferentiated gastric carcinoma (mucin-secreting, signet ring cell carcinoma)

Clinical features

General symptoms

- **In most cases, there are no early symptoms.**
- In advanced stages, the size and growth of the tumor can lead to:
- **Abdominal pain** and **ascites**
- Cancer cachexia
- Possible disruption of menstrual cycle
- Dyspnea due to malignant pleural effusion

- Abdominal or pelvic mass
- Complication: tumor can cause ovarian torsion→ tissue infarction → surgical emergency

The first symptom is often increasing abdominal girth (clothes no longer fit at the waist)!

Specific symptoms

- **Granulosa cell tumor**: Granulosa cells express aromatase (estrogen synthesis occurs in 25% of tumors).
- **Menstrual irregularities** such as postmenopausal bleeding and metrorrhagia
- Increased risk of endometrial cancer
- **Precocious puberty**
- **Sertoli-Leydig cell tumor**: can produce either estrogen or testosterone
- Virilization due to tumor-induced testosterone production:
- Symptoms in females: Amenorrhea, hirsutism, decreased fertility, and acne
- Symptoms in males: Precocious puberty in boys and gynecomastia in men, feminization in males if estrogen is produced
- **Yolk sac tumor, dysgerminoma**: rapid growth, acute onset of symptoms (pelvic mass and pain)
- **Struma ovarii**: symptoms of hyperthyroidism
- **Pseudomyxoma peritonei**
- Bursting of a mucinous cystadenoma/carcinoma may spread tumor cells throughout the peritoneum.
- Mucinous cells cause gelatinous ascites and intra-abdominal adhesions.
- May require several surgical treatments and, in the long term, usually leads to cachexia and death.
- **Meigs syndrome**
- Ascites and pleural effusion in association with an ovarian tumor (e.g., ovarian fibroma)
- In 90% of cases, the ovarian tumor is unilateral.
- The cause is unknown.
- Surgical removal of the tumor leads to a complete resolution of symptoms.

Diagnostics

- Hypercalcemia due to paraneoplastic synthesis of PTHrP
- Tumor markers
- Epithelial ovarian tumor: **CA-125**
- Yolk sack tumor: alpha-fetoprotein
- Non-gestational choriocarcinoma: beta hCG
- Granulosa cell tumor: inhibin B
- Imaging: Transvaginal ultrasound is the gold standard, but abdominal or rectal ultrasound may also be conducted.
- Histology:
- Granulosa cell tumor: Call-Exner bodies (granulosa cells arranged in clusters surrounding a central cavity with eosinophilic secretions, resembling primordial follicles)
- Sertoli-Leydig cell tumor: contain Reinke crystals
- Ovarian fibroma: clusters of spindle-shaped cells (fibroblasts)

Fine needle aspiration cytology is absolutely contraindicated in ovarian tumors because it increases the risk of spreading tumor cells to the peritoneum!

Differential diagnoses

- **Ovarian cysts**
- **Endometriosis**
- **Tubo-ovarian abscess**
- **Ectopic pregnancy**
- Pelvic inflammatory disease

Ultrasound workup of ovarian masses		
	Benign	Malignant
Internal structure	Uniform, thin walls	Irregularly thickened septa
Margins	Smooth	Indistinct borders; papillary projections
Echogenicity	Anechoic	Hypoechoic, anechoic, and hyperechoic components
Content	Cystic	Cystic or solid components
Vascularization	Unremarkable	Possible central vascularization
Pouch of Douglas	Unremarkable	Possible free fluid (ascites)

Treatment

- **Surgery**
- Frozen section and histology positive for carcinoma: radical surgical staging
- Removal of the greater omentum
- Lymphadenectomy
- Hysterectomy with bilateral salpingo-oophorectomy
- Appendectomy if involvement is suspected during surgery
- Biopsy from all noticeable locations/adhesions
- Frozen section negative for carcinoma: tumor resection, but no surgical staging
- **Chemotherapy**
- Indicated for all patients as adjuvant therapy
- First-line therapy: **carboplatin** polychemotherapy and antimitotics (e.g., **paclitaxel**)
- Radiation therapy: rarely used due to the intraperitoneal location and low radiosensitivity of the tumor

Malignant germ cell tumors respond particularly well to polychemotherapy because they are highly aggressive!

Benign tumors of uterus

Fibroid is a commonest benign tumor of the uterus and also the commonest benign solid tumor in female. Histologically this tumor is composed of smooth muscle and fibrous connective tissue, so named as uterine **leiomyoma, myoma or fibromyoma**.
Incidence – at least 20 per cent of women at the age of 30 have got fibroid in their wombs. The incidence of symptomatic fibroid in hospital outpatient is about 3 per cent.
Etiology still remains unclear. The prevailing hypothesis is that, it arises from the neoplastic single smooth muscle cell of myometrium. The possible causes are: chromosomal abnormality (rearrangements, deletions), role of polypeptide growth factors, a positive family history is often present. The growth is predominantly oestrogen-dependent tumour.
Increased risk factors include nuliparity, obesity, hyperoestogenic state, black woman, reduced risk multiparity, smoking.
Uterine fibroids are the most common pelvic tumor, occurring in about 70% of women by age 45. However, many fibroids are small and asymptomatic. About 25% of white and 50% of black women eventually develop symptomatic fibroids. Fibroids are more common among women who have a high body mass index. Potentially protective factors include parturition and cigarette smoking.

Most fibroids in the uterus are

- Subserosal
- Intramural
- Submucosal

Occasionally, fibroids occur in the broad ligaments (intraligamentous), fallopian tubes, or cervix.

Some fibroids are pedunculated. Most fibroids are multiple, and each develops from a single smooth muscle cell, making them monoclonal in origin. Because they respond to estrogen, fibroids tend to enlarge during the reproductive years and decrease in size after menopause.
Fibroids may outgrow their blood supply and degenerate. Degeneration is described as hyaline, myxomatous, calcific, cystic, fatty, red (usually only during pregnancy), or necrotic. Although patients are often concerned about cancer in fibroids, sarcomatous change occurs in < 1% of patients.

Symptoms and Signs

Fibroids can cause abnormal uterine bleeding (eg, menorrhagia, menometrorrhagia).

If fibroids grow and degenerate or if pedunculated fibroids twist, severe acute or chronic pressure or pain can result. Urinary symptoms (eg, urinary frequency or urgency) can result from bladder compression, and intestinal symptoms (eg, constipation) can result from intestinal compression.

Fibroids may increase risk of infertility. During pregnancy, they may cause recurrent spontaneous abortion, premature contractions, or abnormal fetal presentation or make cesarean delivery necessary. Fibroids may also cause postpartum hemorrhage.

Diagnosis

- Imaging (ultrasonography, saline infusion sonography, or MRI)

The diagnosis of uterine fibroids is likely if bimanual pelvic examination detects an enlarged, mobile, irregular uterus that is palpable. Confirmation requires imaging, which is usually indicated if

- Fibroids are a new finding.
- They have increased in size.
- They are causing symptoms.
- They need to be differentiated from other abnormalities (eg, ovarian masses).

When imaging is indicated, ultrasonography (usually transvaginal) or saline infusion sonography (sonohysterography) is typically done. In saline infusion sonography, saline is instilled into the uterus, enabling the sonographer to more specifically locate the fibroid in the uterus.

If ultrasonography, including saline infusion sonography (if done), is inconclusive, MRI, the most accurate imaging test, is usually done.

Treatment

- Sometimes gonadotropin-releasing hormone (GnRH) agonists (analogs) or other drugs for temporary relief of minor symptoms
- Myomectomy (to preserve fertility) or hysterectomy for symptomatic fibroids

Asymptomatic fibroids do not require treatment. Patients should be reevaluated periodically (eg, every 6 to 12 months).
For **symptomatic fibroids,** medical options, including suppression of ovarian hormones to stop the bleeding, are suboptimal and limited. However, clinicians should consider first trying medical treatment before doing surgery. GnRH agonists can be given before surgery to shrink fibroid tissues; these drugs often stop menses and allow blood counts to increase. In perimenopausal women, expectant management can usually be tried because symptoms may resolve as fibroids decrease in size after menopause.

Drugs for fibroids

Several drugs are used to relieve symptoms, reduce fibroid growth, or both:

- GnRH agonists
- Exogenous progestins
- Antiprogestins
- Selective estrogen receptor modulators (SERMs)
- Danazol
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Tranexamic acid

GnRH agonists are often the drugs of choice. They can reduce fibroid size and bleeding. They may be given as follows:

- IM or subcutaneously (eg, leuprolide 3.75 mg IM every month, goserelin 3.6 mg subcutaneously every 28 days)
- As a subdermal pellet
- As nasal spray (eg, nafarelin)

GnRH agonists can decrease estrogen production. They are most helpful when given preoperatively to reduce fibroid and uterine volume, making surgery technically more feasible and reducing blood loss during surgery. In general, these drugs should not be used in the long term because rebound growth to pretreatment size within 6 months is common and bone demineralization may occur. To prevent bone demineralization when these drugs are used long term, clinicians should give patients supplemental estrogen (add-back therapy), such as a low-dose estrogen-progestin combination.

Exogenous progestins can partially suppress estrogen stimulation of uterine fibroid growth. Progestins can decrease uterine bleeding but may not shrink fibroids as much as GnRH agonists. Medroxyprogesterone acetate 5 to 10 mg orally once a day or megestrol acetate 40 mg orally once a day taken for 10 to 14 days each menstrual cycle can limit heavy bleeding, beginning after 1 or 2 treatment cycles. Alternatively, these drugs may be taken every day of the month (continuous therapy); this therapy often reduces bleeding and provides contraception. Depot medroxyprogesterone acetate 150 mg IM every 3 months has effects similar to those of continuous oral therapy. Before IM therapy, oral progestins should be tried to determine whether patients can tolerate the adverse effects (eg, weight gain, depression, irregular bleeding). Progestin therapy causes fibroids to grow in some women. Alternatively, a levonorgestrel-releasing intrauterine device (IUD) may be used to reduce uterine bleeding.

For **antiprogestins** (eg, mifepristone), the dosage is 5 to 50 mg once a day for 3 to 6 months. This dose is lower than the 200-mg dose used for termination of pregnancy; thus, this dose must be mixed specially by a pharmacist and may not always be available.

SERMS (eg, raloxifene) may help reduce fibroid growth, but whether they can relieve symptoms as well as other drugs is unclear.

Danazol, an androgenic agonist, can suppress fibroid growth but has a high rate of adverse effects (eg, weight gain, acne, hirsutism, edema, hair loss, deepening of the voice, flushing, sweating, vaginal dryness) and is thus often less acceptable to patients.

NSAIDs can be used to treat pain but probably do not decrease bleeding.

Tranexamic acid (an antifibrinolytic drug) can reduce uterine bleeding by up to 40%. The dosage is 1300 mg every 8 hours for up to 5 days. Its role is evolving.

Surgery for fibroids

Surgery is usually reserved for women with any of the following:

- A rapidly enlarging pelvic mass
- Recurrent uterine bleeding refractory to drug therapy
- Severe or persistent pain or pressure (eg, that requires opioids for control or that is intolerable to the patient)

- A large uterus that has a mass effect in the abdomen, causing urinary or intestinal symptoms or compressing other organs and causing dysfunction (eg, hydronephrosis, urinary frequency, dyspareunia)

- Infertility (if pregnancy is desired)

- Recurrent spontaneous abortions (if pregnancy is desired)

Other factors favoring surgery are completion of childbearing and the patient's desire for definitive treatment.

Myomectomy is usually done laparoscopically or hysteroscopically (using an instrument with a wide-angle telescope and electrical wire loop for excision), with or without robotic techniques.
Hysterectomy can also be done laparoscopically, vaginally, or by laparotomy.
Most indications for myomectomy and hysterectomy are similar. Patient choice is important, but patients must be fully informed about anticipated difficulties and sequelae of myomectomy vs hysterectomy.

Morcellation is often done during myomectomy or hysterectomy. Morcellation involves cutting fibroids or endometrial tissue into small pieces so that the pieces can be removed through a smaller incision (eg, laparoscopically). Very rarely, women who have surgery for uterine fibroids have an unsuspected, undiagnosed sarcoma or other uterine cancer. If morcellation is done, malignant cells may be disseminated into the peritoneum. Patients should be informed that if morcellation is used, there is a very small risk of disseminating cancerous cells.
If women desire pregnancy or want to keep their uterus, myomectomy is used. In about 55% of women with infertility due to fibroids alone, myomectomy can restore fertility, resulting in pregnancy after about 15 months. However, hysterectomy is often necessary or preferred by the patient.

Factors that favor hysterectomy include

- It is more definitive treatment. After myomectomy, new fibroids may begin to grow again, and about 25% of women who have a myomectomy have a hysterectomy about 4 to 8 years later.

- Multiple myomectomy can be much more difficult to do than hysterectomy.

- Other, less invasive treatments have been ineffective.

- Patients have other abnormalities that make surgery more complicated (eg, extensive adhesions, endometriosis).

- Hysterectomy would decrease the risk of another disorder (eg, cervical intraepithelial neoplasia, endometrial hyperplasia, endometriosis, ovarian cancer in women with a *BRCA* mutation).

Newer procedures may relieve symptoms, but duration of symptom relief and efficacy of the procedures in restoring fertility have not been evaluated. Such procedures include

- High-intensity focused sonography

- Cryotherapy

- Radiofrequency ablation

- Magnetic resonance-guided focused ultrasound surgery

- Uterine artery embolization

Uterine artery embolization aims to cause infarction of fibroids throughout the uterus while preserving normal uterine tissue. After this procedure, women recover more quickly than after hysterectomy or myomectomy, but rates of complications and return visits tend to be higher. Treatment failure rates are 20 to 23%; in such cases, definitive treatment with hysterectomy is required.

Choice of treatment
Treatment of uterine fibroids should be individualized, but some factors can help with the decision:

- Asymptomatic fibroids: No treatment
- Postmenopausal women: Trial of expectant management (because symptoms tend to remit as fibroids decrease in size after menopause)
- Symptomatic fibroids, particularly if pregnancy is desired: Uterine artery embolization, another new technique (eg, high-intensity focused sonography), or myomectomy
- Severe symptoms when other treatments were ineffective, particularly if pregnancy is not desired: Hysterectomy, possibly preceded by drug therapy (eg, with GnRH agonists)

Medical treatment for fibroids and menorrhagia can be achieved by the use of mefenamic acid, tranexamic acid, non-steroidal antiinflammatory drugs (NSAIDs) or antifibrinolytic agents. All are useful medical treatment for menorrhagia, but are not effective in every patient. Commonly in fibroid menorrhagia, one or another of these agents may control bleeding but not the pain. If the pain persists, the patient becomes reluctant to persevere with medical treatment. The luteinizing hormone releasing hormone (LHRH) analogue (goserelin) is used to shrink fibroids and control bleeding by suppressing ovarian function, generally as pretreatment for myomectomy or prehysterectomy for very large fibroids. Decapeptyl 3mg injection on a monthly basis for 6 months or goserelin 3.6mg monthly by injection for the same duration are both acceptable. Patients administered either of these medications should be warned about the side-effect of premature chemical menopause and might need some adback treatment such as tibolone or low-dose estrogens to reduce the disturbing effect of estrogen withdrawal.
The introduction of interventional radiology (**embolization**) has presented a new option for the management of fibroids. In 2004 the National Institute of Clinical Excellence (NICE) provided guidance for clinicians to consider uterine artery embolization for the treatment of fibroids, although it is important to note that currently no concrete data exist pertaining to the effectiveness or outcome of embolization procedures for treatment of fibroid tumors, including the preservation of fertility potential, or the reduction of potential fecundity in patients who wish to conceive. The NICE document comments on indications, means of performance of the procedure, ethics, safety and reduction in mean fibroid volume and blood loss. Counseling and consenting of such women is essential for those who consider this alternative procedure in the management of fibroid uterus. Uterine artery embolization should not be recommended without careful consideration in the treatment of symptomatic uterine fibroids, endometrial polyp or submucosal fibroid.
Women who have had the uterine cavity open during a prior myomectomy should be offered cesarean section when they become pregnant to minimize or avoid the risk of uterine rupture.

Endometrial polyps

Definition
Endometrial polyps are localized tumors within the mucosa of the uterine cavity. Endometrial polyps may be pediculate or sessile, and the size may vary from a few millimeters to 3-4 centimeters.

Occurrence
Endometrial polyps are common findings, both in women with and without gynaecological symptoms. The prevalence of endometrial polyps is reported to be 7.8 % - 34.9 % depending on the population studied.

Symptoms
Most endometrial polyps are asymptomatic. Symptomatic premenopausal women with endometrial polyps most commonly suffer from abnormal uterine bleeding (inter-menstrual bleedings/spotting and/or menorrhagia). Previous studies have reported that the prevalence of endometrial polyps is increased in infertile women, and the results of a randomized controlled trial indicates that removal of endometrial polyps may

improve fertility in infertile women. Postmenopausal bleeding is the most common symptom of endometrial polyps in postmenopausal women.

Aetiology/pathogenesis
The aetiology and pathogenesis of endometrial polyps is unknown. Endometrial polyps are commonly benign. The occurrence of malignant endometrial polyp varies with the population studied, and are reported to be up to 13 %. Postmenopausal women with symptomatic polyps (postmenopausal bleeding) carry the highest risk of malignant endometrial polyp.

Risk factors
- Increasing age (the prevalence increases with age in the reproductive age, it is not known whether the prevalence increases with age in postmenopausal women).
- Obesity
- Use of Tamoxifen
- Hypertension
- A possible association between endometrial polyps and other benign gynaecological conditions such as fibroids, cervical polyps and endometriosis has been reported.

Examinations
Endometrial polyps are diagnosed by transvaginal ultrasound examination, by hysteroscopy or by histological examination. Installation of saline in the uterine cavity increase the sensibility of the examination and is recommended when the occurrence of endometrial polyp is suspected based on ultrasonic findings in women with abnormal uterine bleeding, infertile women and in postmenopausal women. Women with postmenopausal bleeding should be examined within 4 weeks because of a relatively high risk of endometrial cancer (5-10 %). (Please see the guideline entitled ”Postmenopausal bleeding”).

Differential diagnosis
Submucous fibroids.

Treatment
Indications of treatment of women with endometrial polyps are:
- Symptomatic endometrial polyp (most commonly abnormal uterine bleeding)
- Obesity
- Infertility
- In order to exclude malignancy

About 25 % of all endometrial polyps regress spontaneously. Small polyps (< 10 mm) are more likely to regress spontaneously compared to larger polyps. Consequently, small polyps in asymptomatic women without increased risk of malignancy may be left untreated. The risk of malignant endometrial polyp is highest in women with postmenopausal bleeding and in asymptomatic postmenopausal women with larger polyps and other known risk factors for endometrial cancer.
Endometrial polyps should be removed by transcervical resection (hysteroscopy). Treatment of endometrial polyps by curettage is not recommended as the risk of leaving the polyp behind is relatively large.
Transcervical resection of endometrial polyps is effective in women suffering from spotting/inter-menstrual bleedings and postmenopausal bleeding. In women with endometrial polyps and menorrhagia, a concomitant resection of the endometrium in perimenopausal women should be considered in order to reduce periodic blood loss and the risk of recurrent menorrhagia.
When atypical hyperplasia or malignancy is diagnosen by histopathological examination within an endometrial polyp, the woman should be treated in accordance with the guidelines for treatment of atypical endometrial hyperplasia or endometrial cancer, respectively.

Complications
Complications during transcervical resection of endometrial polyps is most frequently related to the dilatation of the cervix in nulliparous and postmenopausal women. Preoperative treatment with local oestradiol is recommended in order to reduce the risk of such complications in postmenopausal women.

Recommendations

- Instillation of saline into the uterine cavity (hydrosonography) is recommended when intrauterine pathology such as endometrial polys are suspected during transvaginal ultrasound examination in women with abnormal vaginal bleeding, infertile women and postmenopausal women.
- Endometrial polyps should be removed in symptomatic women, infertile women and women who have an increased risk of endometrial malignancy.
- Endometrial polyps should be removed by transcervical resection (hysteroscopy). Curettage is not recommended for removal of endometrial polyps.
- Preoperative treatment using local estradiol reduces the risk of complications during transcervical resection of endometrial polyps in postmenopausal women

Endometrial Hyperplasia and Neoplasia

Introduction

By definition, adenocarcinoma of the endometrium is an invasive disease, invading either the endometrial stroma or the underlying myometrium of extrauterine tissues. Most endometrial carcinomas maintain endometrioid differentiation; these also can contain areas of mucinous or squamous differentiation. Other nonendometrioid subtypes seen in routine practice include clear cell carcinoma, papillary serous carcinoma, and other rare variants. According to the US Gynecologic Oncology Group histologic grading system, grade 1, well-differentiated carcinoma, consists of a neoplasm with less than 5% of solid cancer; grade 2, moderately differentiated carcinoma, contains 6–50% solid cancer; and grade 3, poorly differentiated carcinoma, contains more than 50% of solid tumor.

Tumor grading is of greater independent prognostic value for endometrioid endometrial adenocarcinoma and its related types (i.e., endometrial, secretory, mucinous, squamous) than for papillary serous and clear cell adenocarcinomas. Papillary serous and clear cell cancers do not show the grade-dependent changes in aggressiveness seen with the endometrioid tumors; instead, as a group they are consistently aggressive. Division of endometrial adenocarcinomas into the clinicopathologic classes of endometrioid and nonendometrioid types is paralleled further by differences in epidemiologic risk factors and precursor lesions. Type I, or endometrioid, endometrial adenocarcinomas are more frequent in women taking exogenous estrogen and often are preceded by precursor lesions, which is the subject of this discussion.

It has traditionally been suggested that endometrioid endometrial adenocarcinoma is preceded by endometrial hyperplasia (EH). EH previously was considered a continuum of morphologic changes often beginning with simple glandular/stromal overgrowth (simple hyperplasia) and ending with complex, highly atypical histologic and cytologic proliferations, variously referred to as atypical adenomatous hyperplasia, dysplasia, or carcinoma *in situ*. The figure most often cited in the literature for progression of atypical adenomatous hyperplasia to carcinomas was 30% at 10 years.

This hyperplasia model, as defined by the World Health Organization (WHO), was developed primarily by pathologists as a morphologic classification into four classes of hyperplasia, composed of complex or simple architecture combined variously with presence or absence of cytologic atypia. These do not cleanly correspond to four distinctive biologic categories, nor are there comparable numbers of clinical interventions individually matched to each hyperplasia subtype. A contraction of the number of categories to three was suggested by merging all atypical hyperplasia (AH) groups into one diagnostic category (atypical endometrial hyperplasia) which contained the highest endometrial cancer risk. Pathologist scoring of presence or absence of cytologic atypia is notoriously unreliable, and has become a major limitation of this approach. In a Gynecologic Oncology Group study only 38% of community diagnosed atypical endometrial hyperplasia were confirmed as atypical hyperplasia upon central review by a panel of gynecologic pathologists. A further complication of this contraction of diagnostic groups by cytologic atypia alone is the de-emphasis on architectural features which remain of value in stratifying high from low risk subgroups.

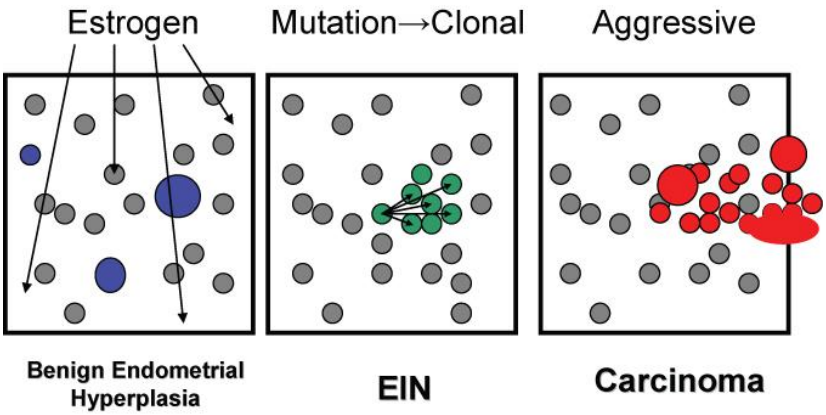
New data that have emerged in the last decade have changed the underlying assumptions upon which endometrial precancer diagnosis is constructed. The assumption of gradual evolution of endometrial histologic patterns across hyperplastic groups is incorrect. Endocrine induced endometrial changes, such as those conferred by unopposed estrogens, do produce a field-wide effect that gradually changes the histologic pattern as a function of time and dose. This can be described as a dynamically changing histotype, which early on has the appearance of a disordered proliferative endometrium, and with subsequent remodeling assumes a variable gland density that we prefer to designate as the benign endometrial hyperplasia sequence. Bona fide premalignant lesions, however, are of an entirely different character. Precancerous lesions of the endometrium originate focally as a result of clonal outgrowth of genetically mutated glands which have a differing cytologic and architectural pattern relative to the background. Their morphology is discontinuous from that of the background endometrium itself, and can only be recognized through a combination of newly defined histologic features which define the entity of endometrial intraepithelial neoplasia (EIN). This is more completely described in the next section.

EIN is not synonymous with carcinoma but indicates a lesion that may regress, persist, or progress to invasion. Approximately one third of women diagnosed with EIN will have a concurrent carcinoma diagnosed within the first year, and the long term cancer risk is 45 times increased beyond benign endometrial hyperplasia.

Morphologically, an altered relationship between glands and stroma distinguishes carcinoma from EIN. Even when present in the patient, myoinvasion is rarely evident in an endometrial curettage or biopsy, which rarely succeeds in sampling the underlying myometrium. For this reason, distinction between EIN and adenocarcinoma must commonly be performed in isolated endometrial samples devoid of myometrium. Within the endometrial compartment itself, examination of stromal quality and character in the region of a glandular lesion is not a reliable indicator of whether the stroma has been invaded. EIN lesions are made up of aggregates of individual glands which may have some branch points, but lack the complex folded sheets that produce a maze of interconnected lumens or villoglandular architecture in some carcinomas. The architectural pattern of the glands is an indicator of an altered interaction between glands and stroma. Functional changes which correspond to malignant behavior *in vivo* include loss of anchorage dependent growth. The histologic equivalent of this feature is growth of epithelial cells without a requirement for contact with a basement membrane. This is evident histologically by areas of solid epithelial growth without lumen formation or a cribriform pattern of multiple gland lumens within a single gland. The presence of myoinvasion, or any one of the above described patterns (solid, cribriform, villoglandular, maze-like), is diagnostic of adenocarcinoma.

Benign endometrial hyperplasia and endometrial intraepithelial lesion

A primary objective of endometrial diagnosis and therapy is distinction between primary hormonal abnormalities having a secondary endometrial effect (the benign endometrial hyperplasia sequence) and intrinsically abnormal neoplastic endometrial glands prone to malignant transformation (EIN). Unopposed estrogen creates field-wide changes in the endometrium, including cyst formation, randomly scattered tubal metaplasia, and remodeling of glands. In contrast, EIN is a clonal proliferation of abnormal endometrial glands which arises at a point in space and spreads peripherally, eventually involving the entire endometrial compartment in approximately a quarter of women at the time of initial EIN diagnosis. The diagnostic, nomenclature, and therapeutic distinctions between these processes are projected into the EIN diagnosis schema which is described below. This is intended to replace, rather than supplement, older classification using the 1994 WHO hyperplasia standards. The application of new diagnostic criteria which were not part of the 1994 WHO descriptions prevents an absolute concordance between the old and new systems. Below we review the expanded evidence base for revised criteria, and summarize diagnostic implemetation strategies.



Topography of hormonal and neoplastic endometrial disease. The diffuse field-wide endometrial effects of unopposed estrogens in benign endometrial hyperplasia are randomly scattered throughout the endometrial compartment and include cysts, and locally variable gland density. EIN lesions arise through local proliferation of genetically mutated glands which are characterized by an altered cytology and gland area exceeding stromal area. Adenocarcinoma has a similar clonal origin (often within a pre-existing EIN lesion) but with solid, cribriform, or maze-like architecture. With time, EIN and adenocarcinoma lesions can expand to occupy the entire endometrial compartment and thus no longer retain their earlier localizing character.

Endometrial precancers first were identified as premalignant lesions by virtue of their temporal and spatial association with cancer in large patient series. Of all women with atypical EH, 25% have an adenocarcinoma at hysterectomy. Although these strategies generally have been successful in defining broad classes of morphologic lesions most likely to be associated with cancer, clinical outcomes are highly insensitive in detection of precancers. A low precancer-to-cancer progression efficiency predicts that most premalignant lesions will never display a malignant end point. Further difficulty in standardizing diagnosis of endometrial precancers comes from poor reproducibility by pathologists of histopathologic criteria used for lesion classification. This situation has spurred development of novel diagnostic strategies applicable to lesional tissues of individual patients that are capable of accurately discriminating between biologic precancers and non-precancers. Even if such a laboratory approach were impractical for everyday use, it would constitute a powerful tool for critical evaluation and refinement of current histologic diagnostic practices.

Monoclonal growth and mutation of tumor-suppressor genes are measurable features of the premalignant phase of endometrial tumorigenesis that can be directly ascertained in paraffin-embedded tissues and correlated with histology on a case-by-case basis. The idea that endometrial precancers are monoclonal proliferative products of a single transformed cell is based on a multistep model of tumorigenesis in which progression is driven by sequentially acquired mutations manifest as altered morphology and increasing aggressiveness. Although initial stages may not show an invasive phenotype, it is anticipated that premalignant lesions have sufficient growth advantage relative to their source tissues that they expand monoclonally. This expansion has now been shown to be the case for putative endometrial precancers using a variety of polymerase chain reaction-based molecular genetic methodologies applied to DNA isolated from targeted regions of paraffin sections: nonrandom X chromosome inactivation, clonal propagation of altered microsatellites in microsatellite-unstable tissues, and clonal propagation of acquired mutations of tumor-suppressor genes such as K-*ras* and *PTEN*. Monoclonal growth seems to be one of the seminal qualities of premalignant tissues at a variety of sites, including the oral mucosa, cervix, skin, stomach, and vulva.

Early stages of carcinogenesis are characterized by incremental growth advantages, which are necessarily small in relation to normal tissues and exquisitely sensitive to environmental modification. Hormonally mediated selection of latent transformed clones is one mechanism that might link genetic and endocrine events in genesis of this disease. This selection may occur through changes in precancer clone proliferation rates or remodeling of adjacent normal tissues. In the case of precancers confined to the functionalis, persistence is enhanced by absence of regular shedding (anovulation). Shedding is also a key part of progestin therapy for precancers because patients who have biopsies before a withdrawal bleed often have persistent lesions, albeit with an altered cytology. For this reason, repeat biopsy for confirmation of postprogestin precancer ablation is best accomplished after a withdrawal bleed to realize the full benefit of shedding and to avoid the confounding effects of progestins on histopathology interpretation.

Multiple marker systems (X inactivation, novel microsatellites) used together are approximately 80% sensitive in detection of monoclonal precancers from paraffin sections, a significant improvement over the 25% sensitivity of precancer detection realized when using a clinical standard of progression to carcinoma. In cases that do have an associated carcinoma, conservation of acquired genetic changes between matched premalignant and malignant tissues has provided a highly specific basis to conclude evolution from the former to the latter. Detailed lineage reconstruction, including hierarchical ordering of steps from precancer to cancer, has been accomplished in cases in which the repertoire of informative genetic markers is sufficiently rich. High cost and technical complexity place a molecular genetic laboratory standard of precancer diagnosis beyond the reach of a routine diagnostic setting.

areful histopathologic study of genotypically ascertained endometrial precancers explains prior problems in diagnosis and provides specific directions for improvement. Close correlations between histopathology and genotype are possible by isolating DNA from delineated regions of a paraffin section, which is also available as a serially sectioned stained slide. Epithelial differentiation of monoclonal precancers is usually endometrioid, but foci of squamous, mucinous, and tubal differentiation may be present. Changes in the hormonal environment, such as progesterone administration, may reduce the degree of cytologic atypia. Although most genetic precancers are diagnosed as atypical EH, poor reproducibility of this diagnosis compromises consistent management and raises the possibility that existing diagnostic criteria are inadequate. A particular void in precancer diagnosis has been absence of informative architectural criteria. Computerized morphometric analysis of monoclonal endometrial precancers, using algorithms that previously were shown to predict relevant clinical outcomes of concurrent or future endometrial adenocarcinoma, has broken this stalemate. When cytologically altered endometrial glands become so crowded that they comprise more than half of the sectioned surface, they predict monoclonality with a sensitivity and specificity at least equal to the clinical judgment of experienced subspeciality gynecologic pathologists. The absolute appearance of EIN cytology varies greatly between individual examples, and not all have the appearance of rounded nuclei with prominent nucleoli that is the classic definition of atypia in this tissue. What is consistent, however, is that the crowded glands of an EIN lesion always have an altered cytology relative to the background endometrium in the same patient. A relative internal, rather than absolute fixed, standard for recognition of altered cytology is the common feature of premalignant endometrial disease and EIN. Size is an important consideration in evaluation of a localizing lesion, such as an emergent EIN. A threshold of clinical relevance is when the crowded focus (areas with gland area exceeding stromal area) of cytologicially altered glands reaches a maximum dimension greater than 1 mm within a single fragment. Smaller lesions are not necessarily associated with heightened cancer risk, and should not be diagnosed as EIN.

The term *endometrial intraepithelial neoplasia* accurately describes endometrial precancers because monoclonal origin from a single transformed cell is the pathognomonic feature of all neoplasms. The superb performance of computerized morphometric analysis in classifying all genetically and clinically defined precancers into one group reaffirms the feasibility of using routine hematoxylin and eosin–stained tissue sections to define a singular category of precancers.

Classification of endometrial disease based on lesion biology aspires to place all precancers into a single group (EIN) and in contrast with mutually exclusive entities corresponding to different management options. Introduction of refined precancer diagnostic criteria, such as volume percentage stroma (VPS) (that function of the sectioned tissue occupied by stroma), may improve histopathologic resolution between benign anovulatory (BEH) and premalignant (EIN) disease.

There are now several large clinical outcome studies outlining the clinical outcomes of patients diagnosed with EIN. There is a high rate of concurrent occult carcinoma in women diagnosed with EIN by biopsy. In a large GOG trial in which 153 women with EIN underwent hysterectomy, 36% (56) were found to have carcinoma. This is concordant with a retrospective pathology review study in which 39% of women diagnosed with EIN developed adenocarcinoma within the first year. In addition to this high rate of concurrent adenocarcinoma which is not evident from the initial EIN-containing biopsy, there is a 45-fold increased risk of developing carcinoma after the first year.

The relatively low risk of benign endometrial hyperplasia compared to EIN is evident in a study of over 600 women with various "endometrial hyperplasias" which were stratified as EIN vs. benign (usually estrogen

effect, or benign endometrial hyperplasia sequence). The results shown in the figure indicate a very high negative predictive value for absence of cancer outcomes in women with benign endometrial hyperplasia.

Clinical management of EIN is similar to that previously applied to a diagnosis of atypical endometrial hyperplasia. In the US this is usually hysterectomy. There is a clinical need for nonsurgical alternative therapies in women who wish to retain fertility, or are poor surgical candidates, but there is a paucity of clinical trail data on the subject. High dose progestin therapy can succeed in ablating some EIN lesions, but, because of the high concurrent cancer rate and unpredictable response, must be accompanied by careful clinical surveillance.

Risk indicators for endometrial cancer and precursors

Age ≥60 years
Obesity (with upper body fat pattern)*
Estrogen-only replacement therapy
Previous breast cancer
Tamoxifen therapy for breast cancer
Chronic liver disease
Infertility
Low parity
Chronic anovulation (polycystic ovarian disease, estrogen secreting ovarian stroma or tumors)

*With or without diabetes and hypertension.

Screening and diagnostics

In the case of endometrial carcinoma, the current consensus among experts in the field of periodic health examinations is not to recommend screening for endometrial cancer and its precursors because there is no scientific evidence to support such examinations in menopausal and postmenopausal women. The arguments against screening for endometrial carcinoma are as follows:

1. Although endometrial carcinoma is common, morbidity rates are low, comparatively less important in number than breast carcinoma, colon carcinoma, lung carcinoma, leukemia, lymphoma, brain carcinoma, pancreas carcinoma, and ovary carcinoma.
2. Based on the incidence of endometrial carcinoma in asymptomatic women, it would take about 1000 procedures to detect a single case of either a carcinoma or its precursor, atypical hyperplasia (AH).
3. The techniques available for diagnosing endometrial disease in asymptomatic women suffer from pitfalls in interpretation or instrumentation. One is the difficulty in interpreting relatively inexpensive cytologic material; the other is that office biopsy aspiration techniques are relatively expensive and uncomfortable to painful, and tissue insufficient for diagnosis rates may be 25%.
4. No controlled randomized trials have been done to evaluate the effectiveness of screening in endometrial carcinoma. Even in high-risk menopausal women, screening would detect only 50% of all cases of endometrial carcinoma.
5. Most patients with disease eventually become symptomatic (i.e., presenting with abnormal uterine bleeding, yet have early clinical stage disease at the time of surgical diagnosis and treatment). This contention is supported by the excellent 5-year survival rates of patients with stage I endometrial carcinoma (i.e., 80–91%). The clinicopathologic and epidemiologic data suggest that about 80% of endometrial carcinomas are slow growing with a favorable course, and earlier treatment of asymptomatic carcinomas would be no more effective than treatment given when symptoms appear.
6. Elderly people are difficult to enroll into screening programs, and the dropout rate is relatively high. This is particularly true if painful techniques are used for endometrial evaluation.
7. The incidence of endometrial carcinoma and its precursors is low in women aged younger than 50 years and in women receiving combination-type HRT (estrogen/progestins).

Screening for endometrial carcinoma or its precursor, EIN, in asymptomatic, postmenopausal women is presently not recommended because of the low incidence of endometrial carcinoma in this group of women, estimated to be 1.7 cases per 1000 women per year, and the low prevalence, in the order of 1 per 1000 women.[36] In the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, no patients developed endometrial carcinoma while on daily estrogen-only replacement therapy, 0.625 mg, during a follow-up of 36 months versus 1% of women who developed endometrial carcinoma on placebo. The average age of women with EIN is 52 years, which is about 8 years earlier than the average age of 60 for endometrioid endometrial adenocarcinoma in the same patient population. The interval for progression from EIN to adenocarcinoma can be more directly estimated in individual patients who undergo protracted surveillance following an EIN diagnosis. Once patients with concurrent adenocarcinoma are excluded (defined as cancer found within the first year of follow-up), the average interval to diagnosis of adenocarcinoma is 4 years.

Who should be screened?

Women receiving unopposed estrogens need endometrial sampling once every 2 years (relative risk increases only after 2 years of estrogen use), particularly if endometrial hyperstimulation has been documented previously and has not been treated by short-term administration of progestins. Also, if the informed, high-risk individual requests an endometrial evaluation before or during HRT or at any time during her periodic health examinations, she should not be deprived of an office-based investigative procedure to rule out endometrial pathology. An endometrial evaluation also should be performed in women at high risk for endometrial carcinoma, such as women with history of Lynch II syndrome.

The term *diagnosis*, as opposed to *screening*, refers to the application of a test to women presenting with symptoms (most commonly abnormal uterine spotting or bleeding) that presumably are related to endometrial carcinoma or its precursors. A study addressed the optimal evaluation strategy for patients with a first period of postmenopausal bleeding at various risks for endometrial carcinoma and AH. Among four options—office endometrial biopsy, dilation and curettage (D&C), hysterectomy, and observation alone (unless bleeding recurred)—office biopsy with the Vabra technique was the most cost-effective initial means, costing less than $41,000 US per year of life saved for patients with a 10% risk of having endometrial carcinoma or AH. For patients at 5% risk, the cost of endometrial biopsy increased, however, to $66,000 US per year of additional life saved for 60-year-old patients. Neither D&C nor hysterectomy was as cost-effective as office biopsy as an initial diagnostic evaluation procedure in patients with any risk for carcinoma/AH and abnormal uterine bleeding. Based on this decision-analytic model, the patient's age and the risk for endometrial carcinoma/AH seem to be important determinants for the use of a given endometrial evaluation technique.

Screening and diagnostic techniques

At present, seven methods exist for assessing the endometrium: cervical/vaginal cytology, endometrial cytology, endometrial biopsy, transvaginal ultrasonography (TVUS), magnetic resonance imaging, hysteroscopy, and D&C.

CERVICAL/VAGINAL CYTOLOGY

The main drawbacks of this method are that it detects mainly advanced endometrial carcinoma and has a high false-negative rate (80%) in postmenopausal, asymptomatic endometrial carcinoma patients. In one study, the odds ratio of endometrial carcinoma in symptomatic postmenopausal women was three times greater in the presence of histiocytes with phagocytosis of acute inflammatory and red blood cells compared with controls.[45] Histiocytes alone failed to predict either endometrial carcinoma or hyperplasia. Endometrial cells on cervical smears carried a fourfold odds ratio for EH. Vaginal cytology may detect recurrent cancer in women treated for endometrial carcinoma. Because the risk of recurrence of endometrial carcinoma (11–17%) and adjunct radiotherapy complications (70%) are greatest during the first 3 postoperative years and because most patients with recurrence are symptomatic and only few survive their recurrent disease, annual follow-up examination that includes vaginal cytology is sufficient.

It is generally accepted that the best yield is obtained with tests that directly sample the endometrial lining.[38] Numerous endometrial cell samplers are available commercially. Most of them obtain cellular samples either by brushing or by aspirating the superficial endometrial mucosa. All endometrial cell samplers have been used under experimental conditions; the results in detection rates do not represent detection rates at

large. Nevertheless, if cytologic atypia is the only feature to look for, endometrial cytology may be highly accurate in distinguishing carcinoma from normal or hyperplasia without cytologic atypia. In one study, endometrial cytology using plastic brushes yielded 79% sensitivity, 95.4% specificity, and 80.5% negative predictive value. If the smear contains normal endometrial cells, the patient may have either a normal or a hyperplastic uterine lining. Often, hyperplasia without cytologic atypia is indistinguishable from normal proliferative endometrium. Because this form of hyperplasia is not a carcinoma precursor, however, the patients with symptoms such as uterine bleeding can be treated conservatively. Most cytologic laboratories lack expertise for distinguishing cytologic atypia related to neoplasia from atypia associated with degeneration or repair. As a result, false-positive rates may be too high to justify the routine use of cytology for endometrial disease. Also, the screening of an endometrial smear is time-consuming, and interpretation is difficult because of the complexity of endometrial gland cell morphology. Many carcinoma mimics lead to false-positive results.

At present, histologic sampling is the best means to diagnose either asymptomatic or symptomatic (abnormal uterine bleeding) endometrial neoplasia. Plastic disposable or metal reusable devices using brushing, aspiration biopsy, suction curettage, or stroke biopsy have been used with similarly high diagnostic accuracy. The pitfalls of histologic methods lie in their relatively high cost and degree of discomfort. The latter leads to low compliance rates for repeat testing. Conventional curettage is much too costly yet not 100% foolproof as far as diagnostic accuracy is concerned. According to current experience including our own, the endometrial devices that seem to be the most cost-effective and are associated with the least discomfort for patients are the endometrial aspirators. In cases in which tissue is not obtained with one of the low-vacuum, suction-type aspirators, particularly in an elderly postmenopausal woman whose endometrium is more often than not atrophic, aspirators with a powerful vacuum suction force (e.g., Vabra aspirator; Tis-u-Trap; or sharp-bladed, four-stroke biopsy curette) provide diagnostic tissues.

Although some physicians had success in using endometrial brushes such as the Gynecyte (Looper Surgical, Inc; European version of Endocyte) for cytologic sampling of the endometrium, most prefer to sample the endometrium for histology. The instrument used most frequently is the endometrial Pipelle (Sepal, Boston, MA) and, when appropriate, the Kevorkian curette (EuroMed, Redmond, WA) for histologic sampling in asymptomatic and symptomatic women at risk for endometrial carcinoma and its precursors. In about 10% of postmenopausal women, the endometrial cavity is difficult or impossible to penetrate because of severe stenosis of the external/internal os or because of internal os spasm. In these cases, placing the patient on sequential cyclic therapy with conjugated estrogens (Premarin) (0.625 mg for 25 days) and medroxyprogesterone (Provera) (5 mg for 11–12 days) for 3 consecutive months often results in adequate dilation of the external/internal os to allow penetration of the endometrial cavity. Another alternative is to perform TVUS and assess the thickness of the endometrium (see Transvaginal Ultrasonography below). Finally, traction of the uterus with the endocervical Emmett's tenaculum or a skin (Iris) hook is of considerable help for entering the endometrial cavity in the office. If an endometrial aspirator of the Pipelle type is used, it is important to move and rotate the cannula under negative action suction force within the endometrial cavity at least six times to sample the greatest surface area of the endometrium. In a comparison of the Pipelle versus the Vabra aspirator, the percentage of endometrial surface mucosa sampled with the Pipelle was 4.2% versus 42% with the Vabra aspirator and 60% with D&C under general anesthesia. The difference in percentages of area sampled is likely due to the comparatively greater suction force of the Vabra than the Pipelle device.

Sampling for histology: a step-by-step guide

1. Bimanually examine the uterus to determine its position.
2. Clean the cervix and vagina with acetic acid or other aseptic solution.
3. Insert an Emmett's tenaculum or iris hook into the outer one third of the endocervical canal and pull gently to obtain traction of the uterus.
4. Insert an endometrial aspirator into the endocervical canal. When the aspirator is at the lower uterine segment level, push and rotate it to facilitate entering the endometrial cavity.
5. When it is at the fundus, pull the plunger back rapidly and completely in the cannula to create a high negative pressure gradient.
6. Move the cannula back and forth 6–12 times in the endometrial cavity and rotate it at the same time.
7. Remove the cannula with the plunger pulled back (retain suction) from the endometrial cavity. Empty the material on a lens paper by pushing the plunger forward and place it in 10% buffered formalin tissue fixative.

If little or no tissue is obtained, the procedure can be repeated once. If still no tissue has been obtained, endometrial sampling can be performed using either the Vabra or other powerful aspirators or a metal curette. If still no tissue is obtained and the uterus is small, one can assume endometrial atrophy or fibrous pedunculated polyps are present. Transvaginal sonography or hysteroscopy, if the patient is symptomatic, may be performed.

In current practice, staging of endometrial carcinoma is surgical (hysterectomy, bilateral salpingo-oophorectomy, and pelvic node biopsy) and includes the histologic assessment of invasion of the endocervical mucosa (International Federation of Gynecology and Obstetrics [FIGO] stage IIA) versus the stroma (FIGO stage IIB) in the hysterectomy specimen. As a result, the preoperative evaluation of the endocervical canal is no longer necessary. The exception to the rule is a younger, premenopausal woman in whom a fractional sampling of the uterus can determine whether the patient has an endocervical or an endometrial primary tumor.

TRANSVAGINAL ULTRASONOGRAPHY

TVUS can visualize the endometrium on a monitor when a 5-MHz probe is placed against the vaginal fornix. The thickness of the endometrium can be measured with precision because the endometriomyometrial junction has a distinct halo-like appearance. TVUS is highly sensitive but also has high false-positive rates (low specificity) for identifying endometrial carcinoma. Studies suggested that specificity may be improved without jeopardizing sensitivity rates if the cutoff values were based on length of time since menopause. When the endometrial thickness is 4 mm for women less than 5 years since menopause and 3 mm for women more than 5 years since menopause, TVUS had a 97.4% sensitivity, 75.7% specificity, and 99.7% negative predictive value. With respect to TVUS, the cutoff points for a minimum thickness have varied from one country to another. However, there is consensus that the mean double endometrial thickness in cases of endometrial hyperplasia/carcinoma is significantly greater than that in patients without such lesions. In the USA, the recommended lower limit of finding endometrial cancer is 4 or 5 mm, and at 3 mm, it is not necessary to perform endometrial biopsy.

MAGNETIC RESONANCE IMAGING

At present, magnetic resonance imaging and computed tomography have been proved to be useful for obtaining preoperative data on the extent and depth of myometrial invasion by endometrial carcinoma rather than in the primary diagnosis of endometrial carcinoma and its precursors. Its role in the primary diagnosis of endometrial cancer and its precursors remain to be determined.

HYSTEROSCOPY

The value of hysteroscopy in the diagnosis and directed biopsy of a variety of intracavitary or endometrial lesions in women with postmenopausal bleeding has been extensively documented. If insufficient tissue is obtained on suction curettage, or if a patient continues to have abnormal bleeding, a formal D&C is often recommended, despite the fact that its superiority over office procedures in the diagnosis of cancer has not been established.

Absolute indications for hysteroscopy have not been established. When available, however, hysteroscopy is indicated in any woman with abnormal uterine bleeding in whom an intrauterine abnormality is suspected. Other indications include recurrent miscarriages, infertility caused by endometrial pathology, removal of an impacted intrauterine device, and suspected submucous leiomyomas before abdominal myomectomy. Hysteroscopy is contraindicated in the presence of active infection and intrauterine pregnancy. Active bleeding is a relative contraindication to office hysteroscopy only because blood interferes with vision if carbon dioxide is used as a distending medium. In patients who have severe medical problems, it is prudent to perform hysteroscopy in an outpatient setting where full monitoring and resuscitation facilities are available.

DILATION AND CURETTAGE

D&C essentially has been replaced by office-based endometrial biopsy using flexible aspiration devices. The latter is more cost-effective than D&C, and the diagnostic yield in symptomatic and asymptomatic women is similar to D&C with sensitivity and specificity rates of 90% and 95%. Cervical stenosis prevents successful endometrial sampling in about 10% of cases.

FALSE-NEGATIVE HISTOLOGY

Even direct sampling of the endometrium for histology may fail to detect adenocarcinoma. In several studies, D&C under general anesthesia missed 10% of endometrial carcinomas. This is not surprising for, as was stated earlier, only 60% of mean surface area is sampled with D&C versus 40% for Vabra curettage and 4% for endometrial biopsy with the Pipelle endometrial aspirator. Others found four of 86 (4.6%) women with postmenopausal bleeding with endometrial carcinoma who had either a negative endometrial biopsy result or D&C within 2 years before cancer diagnosis. In another study from Australia, the false-negative rate of endometrial biopsy of focal adenocarcinomas of the endometrium was 47%.

Treatment

Management depends on whether the underlying disease is primarily hormonal (benign endometrial hyperplasia) or intrinsic premalignant disease (EIN). The choice of surgical or hormonal therapy depends on the histopathologic diagnosis, the reproductive status of the woman, whether the patient is on estrogen-only replacement therapy, and her general health. In general, EIN is managed using algorithms that have been previously developed for treatment of atypical endometrial hyperplasia, and benign endometrial hyperplasia using those previously employed for non-atypical hyperplasias. The high cancer risk conferred by an EIN diagnosis, including a 36% incidence of occult carcinoma of which one third are myoinvasive, must be carefully considered in deciding upon appropriate therapy. Although some cases of EIN/early intramucosal adenocarcinoma respond to exogenous progestogens, ovulation inducers, or both, in most cases the lesions tend to recur within a few months to a few years after delivery of the newborn. Medical hormone therapy is also given to women whose general health is unsuitable to withstand surgery.

Benign endometrial hyperplasia responds well to medroxyprogesterone acetate (MPA), 10 mg orally, or micronized progesterone, 300 mg orally, once a day for 14 days per month for 3 months. Such cyclic regimens lead to withdrawal bleeding; a biopsy specimen is obtained at the end of the progestin therapy at 3–4 months. Complete responders should be maintained on cyclic progesterone therapy or, if appropriate, combined cyclic or continuous HRT. If a partial response is obtained, another 3-month trial with MPA, 10 mg orally four times per day, or megestrol acetate, 80 mg, for 3 months may be carried out. Nonresponders and patients with intractable breakthrough bleeding may have transabdominal hysterectomy. Progestin therapy for premenopausal women with EIN calls for larger doses of MPA, 100 mg orally daily; megestrol acetate, 160 mg; or 1 g/week of MPA intramuscularly for 12 weeks. In recent years, another means to treat endometrial hyperplasia with or without atypia has been the medicated intrauterine device (IUD) such as the LNG-(levonorgestrel) releasing intrauterine system (Mirena®, Bayer Healthcare Pharmaceuticals, Inc. Wayne, NJ, USA). Several studies have shown complete response (reversal of endometrial hyperplasia to progestational-type endometrium) ranging from 25 to over 90%. In general, EH responds better (90–100%) than EIN (67–88%) to intrauterine LNG. In addition to the powerful progestational effect of Mirena on the endometrium, adverse events (side effects) that are commonly experienced by patients with oral progestational therapy are considerably reduced. This is because the systemic absorption of LNG is considerably reduced compared to oral progestational therapy. The biopsy specimen should show progestational-type endometrium with marked stromal decidualization. Careful follow up surveillence, including repeated biopsy at approximately 6 month intervals until several are free of disease is advised to ensure complete ablation. Induction of ovulation should follow the progestational therapy.

Surgery (i.e., transabdominal hysterectomy) with or without bilateral salpingo-oophorectomy is recommended for women who have persistent benign endometrial hyperplasia but are symptomatic (abnormal uterine bleeding) and women in the postreproductive age group with EIN. Surgery is justified in this group in the face of 25–35% progression rates to invasion and an 80% failure rate to respond to progestational therapy.[60] Women who develop benign endometrial hyperplasia during estrogen-alone replacement therapy may benefit from the addition of progestins into their replacement regimen. The rare patient (1%) who develops benign endometrial hyperplasia while on combined cyclic or continuous HRT may benefit from either higher doses of combined HRT or simply switching to a progestin-only replacement therapy for 3 months to attempt reverting the hyperplastic endometrium to normal.

It has been shown that duration of progestin administration is crucial for inhibiting endometrial mitotic activity; this is important because control of endometrial growth is primarily related to control of epithelial mitotic activity. Inhibition of endometrial mitotic activity is noted after 11 days of progestin treatment. The most frequent hormone preparations used for medical treatment of evaluated hyperplasia with or without atypia are presented below.

Treatment regimens by type of hormone, dosage, and duration*

	Endometrial Histology	
Hormone Preparations	**Benign Endometrial Hyperplasia**	**EIN**
Medroxyprogesterone acetate	10 mg PO × 14 days/month	100 mg PO or 1000 mg/week IM
Micronized progesterone	300 mg PO × 14 days/month	300 mg/day PO
Megestrol acetate	80 mg PO × 14 days/month	160 mg/day PO
LNG-IUD	20 μg/day x 6 months to 2 years	

IM, intramuscularly; PO, orally; LNG, levonorgestrel.
*All regimens are given for 3 months.

Conclusions

Invasive carcinoma of the endometrium is preceded by EIN, which by genetic markers is monoclonal and morphologically is identified by significant cytologic change relative to the same patient's background endometrium within a region of glands in which gland area exceeds stromal area. Benign endometrial hyperplasia is not a carcinoma precursor lesion, but rather it is an endometrial response to an abnormal hormonal environment of unopposed estrogens.

Although endometrial carcinoma and its precursors are significant because of their morbidity, mortality resulting from carcinoma is low. As a result, mass screening for asymptomatic endometrial carcinoma and its precursors is not cost-effective and is not recommended. Nevertheless, if screening for endometrial carcinoma is desired in a private practice, it should focus on women aged 55 years old and older and women with high carcinoma risk indicators.

Cytologic sampling of the endometrium directly is limited to communities in which cytologic expertise is available. The most often used method to evaluate the endometrium is histology; to reduce cost, it should be carried out in the office, and the device used should employ vacuum suction force, be disposable, and be of low cost. TVUS seems to be a potentially useful alternative to histology for screening and diagnosing endometrial carcinoma and hyperplasia. Hysteroscopy is the diagnostic method of choice for patients in whom office biopsy and TVUS failed to provide a definite diagnosis. Patients with EH without cytologic atypia and patients with atypia who desire to conceive should have progestational therapy. Patients with atypia or intractable uterine bleeding without atypia benefit from hysteroscopy.

CIN

Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignant cervical disease that is also called cervical dysplasia or cervical interstitial neoplasia or cervical squamous intraepithelial lesions (CSIL).

The nomenclature in use in the past was mild, moderate, and severe dysplasia, these were the terms used to describe premalignant squamous cervical cellular changes. Although still in use by some, it has generally been replaced by the term Cervical Intraepithelia Neoplasia(CIN), which is used to describe histologic changes on the uterine cervix. The trend is now tending towards the use of Squamous Intraepithelia Lesions(SIL).

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that is diagnosed by histology as CIN1, CIN2, or CIN3. If left untreated, CIN2 or CIN3 (collectively referred to as CIN2+) can progress to cervical cancer. It is estimated that approximately 1–2% of women have CIN2+ each year, with higher rates reported for women of HIV-positive status, at 10% (2–6). A diagnosis of CIN2+ is an histological diagnosis obtained from biopsies of the suspect lesions, either with or without colposcopy, for which treatment is recommended. Adenocarcinoma in situ (AIS) is a precursor lesion for cervical cancer that is diagnosed by cytology and can be treated. The majority of AIS are found in the transformation zone. AIS may be associated with CIN. There are three principal treatments available in low- and middle-income countries to treat CIN: cryotherapy, large loop excision of the transformation zone (LLETZ, or LEEP), and cold knife conization (CKC).

Definition

It is a potentially premalignant transformation and abnormal growth (dysplasia) of squamous cells on the surface of the cervix. CIN is not cancer, and is usually curable. Most cases of CIN remain stable, or are eliminated by the host's immune system without intervention. However a small percentage of cases progress to become cervical cancer, usually cervical squamous cell carcinoma (SCC), if left untreated.

It can actually be defined as a spectrum of intraepithelial changes (dysplasia) with indistinct boundaries that begins with mild atypia and progresses through stages of more marked intraepithelial abnormalities to carcinoma in situ if untreated or managed.

Dysplasia is a potentially reversible change characterized by an increase in mitotic

Dysplasia is a potentially reversible change characterized by an increase in mitotic

Dysplasia is a potentially reversible change characterized by an increase in mitotic rate, atypical cytologic features (size, shape, nuclear features) and abnormal organization (cellularity, differentiation, polarity) that fall short of invasive carcinoma (premalignant change). Dysplasia may progress to cancer and dysplastic changes may be found adjacent to foci of cancer.

Epidemiology

Population distribution of cervical intraepithelial neoplasia/dysplasia resembles the epidemiology of an infectious disease that is sexually transmitted. Multiple male sexual partners, early age at first sexual intercourse and male partner with multiple previous/current female sexual partners are very important risk factors.

Incidence

The estimated annual incidence in the United States of CIN among women who undergo cervical cancer screening is 4 percent for CIN 1 and 5 percent for CIN 2,3. High grade lesions are typically diagnosed in women 25 to 35 years of age, while invasive cancer is more commonly diagnosed after the age of 40, typically 8 to 13 years after a diagnosis of a high grade lesion. Between 250,000 and 1 million American women are diagnosed with CIN annually. Women can develop CIN at any age, however, women generally develop it between the ages of 25 to 35.

In developing Nations like Nigeria the mean age for cervical intraepithelial neoplasia (CIN) was 37.6 years. CIN I accounted for 3.6%, CIN II 0.8% and CIN III was only 0.4%.The combined prevalence was 48 per 1000.The peculiarity of the developing nations result is the poor uptake or use of screening methods.

In view of the fact that CIN is a premalignant or precursor of cervical cancer it is pertinent to briefly see the incidence and prevalence of this disease condition. Cervical cancer is second only to breast cancer in its incidence world wide. Cancer registry data shows that that there are approximately 400,000 new cases of cervical cancer and 200,000 deaths from this disease every year.

The incidence rate varies from country to country with eighty percent (80%) of the cases occurring in less developed countries. The reasons for this may lie in the socio economic conditions that prevail in these

countries where facilities for family planning, obstetric and gynaecological health care are scarce and cervical screening programmes are virtually non existent.

Cervix-normal histology

Most of the cervix is composed of fibromuscular tissue. The Epithelium is either squamous or columnar.

The **endocervix** is lined by columnar epithelium that secretes mucus this epithelium has complex infoldings that resemble glands or clefts on cross section and the mucosa rests on inconspicuous layer of reserve cells.

The **ectocervix** (exocervix) is covered by nonkeratinizing, stratified squamous epithelium, either native or metaplastic; has basal, midzone and superficial layers. After menopause and in prepubertal girls the superficial layer becomes atrophic with mainly basal and parabasal cells with high nucleo-cytoplasmic ratio that resembles dysplasia.

Squamocolumnar junction: where squamous and glandular (columnar) epithelium

Squamocolumnar junction: where squamous and glandular (columnar) epithelium meets this a major land mark in cervical dyplasia,it is usually in exocervix.The nearby reserve cells are involved in squamous metaplasia, dysplasia and carcinoma.

Transformation zone: also called ectropion, between original squamocolumnar junction and border of metaplastic squamous epithelium; epidermalization and squamous differentiation of reserve cells transform this area to squamous epithelium; site of squamous cell carcinomas and dysplasia.

In the cervix a lot of metaplasia takes place which was what encouraged a lot of study to be conducted.

- Metaplasia is the name given to the process by which one fully differentiated type of epithelium changes into another.
- It is usually an adaptive change which occurs in reaction to longstanding (chronic) irritation of any kind, or in response to hormonal stimuli.
- Metaplastic change is reversible and theoretically transformed epithelium should revert to its original form after the stimulus is removed but this does not always happen.
- Metaplasia occurs at many body sites eg gastric mucosa, bladder,bronchi etc. The

metaplastic process has been extensively studied in the cervix.

The Clinical significance of squamous metaplasia in the cervix is that, this area of the cervical epithelium has under gone metaplasia(Transformation zone) and all the immature metaplastic are susceptible to carcinogens. In view of the afore mentioned it is not surprising that most cervical cancers arise here.

Histology:

Basal cells (reserve cells): cuboidal to low columnar with scant cytoplasm and round/oval nuclei; acquire eosinophilic cytoplasm as they mature; positive for low molecular weight keratin and estrogen receptor; negative for high molecular weight keratin and involucrin.

Suprabasal cells: have variable amount of glycogen, detectable with Lugol/Schiller's test (application of iodine).

Glandular epithelium: positive for estrogen receptor.

Aetiology

Human papillomaviruses (HPV) are members of a family of viruses known as the Papovaviruses. They are epitheliotropic viruses which promote cell proliferation which results in the development of benign papillomatous lesions of the genital tract upper respiratory tract, digestive tracts and cutaneous lesions of the skin. More than 70 distinct HPV types have been identified as a result of molecular hybridisation of DNA extracted from condylomata or warty lesions from a variety of sites. Each virus type has a very restricted site of infection and viruses which occupy similar niches appear to be genetically related. Molecular hybridisation of anogenital warts and cervical biopsies have shown that about 30 of the 70 distinct types of HPV are confined to the female genital tract.

DNA analysis of anogenital warts, CIN and cervical cancerous tissue has shown that two groups of HPV can be identified in the female genital tract. One group of HPV is almost always associated with low grade CIN lesions and exophytic anogenital warts which have a **low risk** of progressing to cervical cancer (HPV type 6, 11, 42, 44, 53, 54, 62, 66). A second group of viruses is found most commonly in CIN2 and CIN3 which have a **high risk** of developing into invasive cancer (HPV type 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68).

The major cause of CIN is chronic infection of the cervix with the sexually transmitted human papillomavirus (HPV), especially the high-risk HPV types 16 or 18 (viruses from the high risk group (HPV16 and HPV 18) have the ability to immortalise primary human keratinocytes ie extend their lifespan) In comparison viruses from the low risk group (HPV-6 and HPV -11) do not extend the life span of transfected human cells which mature and die at the same rate as non infected cells. Similarly the low risk viruses perform poorly in experiments concerned with the malignant transformation of rodent cells in comparison to the high risk HPV types. Moreover, HPV-16 and HPV -18 infected human keratinocytes in raft culture (an organotypic culture medium) exhibit a differentiation pattern very similar to that seen in vivo in CIN. Over 100 types of HPV have been identified. About a dozen of these types appear to cause cervical dysplasia and may lead to the development of cervical cancer. Other types cause warts.

The viral DNA Integration is a consistent finding in all cancers harbouring the high risk virus types HPV16 and HPV18 and provides the strongest evidence that HPV16 and HPV18 play an important role in the development of cervical cancer. HPV DNA is present in 90% of all cervical invasive cancer.
It is not sufficient to say that simple infection with high risk HPV or even integration of HPV 16 /18 into the host cell nucleus is enough for malignant transformation of the cervical epithelium. Obviously Infection of the genital tract with HPV 16 is relatively common whereas invasive cancer is rare; and integration has been detected in some cases of genital warts and CIN lesions. A number of associated-factors have been proposed such as impaired immune response, persistence of virus, smoking and administration of steroid hormones (as oral contraceptives). Other genetic events such as loss of tumour suppressor genes and the activation of oncogenes may also play a role. Mutations in ras ,fos and other oncogenes have been detected in cervical cancer cell lines but their role in vivo is still to be determined. The knowledge of HPV infection has made a remarkable improvement in the screening, diagnosis, treatment, prevention and prognosis of cancer of the cervix.
The **host immunity** plays a significant role in the control of this disease entity. The fact that HPV remains localised to cervix and vagina further indicates that local immune responses are sufficient in controlling and resolving HPV infection. Both cell mediated immunity and humoral immunity. Also immunosuppression has been implicated as an associated factor. The majority of infections are transient and not clinically evident with 70-90% of infections clearing within 12-30 months. This suggests that host immunity is generally able to clear HPV infection.

Histopathological features
Abnormal cellular proliferation, maturation and atypia characterize cervical intraepithelial neoplasia(CIN). Nuclear abnormality is the hallmark of CIN and includes hyperchromasia, pleomorphism, irregular borders, and abnormal chromatin distribution. These nuclear abnormalities persist throughout the epithelium irrespective of cytoplasmic maturation towards the surface. Mitotic rate is increased and abnormal mitotic figures may be seen.
Histologic grading of CIN is based on the proportion of the epithelium occupied by dysplastic cells. The epithelium is divided into thirds.

Grading
CIN 1 is considered a low grade lesion. It refers to mildly atypical cellular changes in the lower third (basal 1/3) of the epithelium (formerly called mild dysplasia/Abnormal cell growth). HPV viral cytopathic effect (koilocytotic atypia) is often present. This corresponds to infection with HPV, and typically will be cleared by immune response in a year or so, though can take several years to clear.
CIN 2 is considered a high grade lesion. It refers to moderately atypical cellular changes confined to the basal two-thirds of the epithelium (formerly called moderate dysplasia) with preservation of epithelial maturation.
CIN 3 is also considered a high grade lesion/Severe dysplasia. It refers to severely atypical cellular changes encompassing greater than two-thirds of the epithelial thickness, and includes full-thickness lesions (formerly called severe dysplasia or carcinoma in situ).
Cytologic grading of CIN also uses a three-tier system. However, the new Bethesda System for cytological diagnosis divides precursors of cervical squamous cell carcinoma into **low-grade squamous intraepithelial lesion** and **high-grade intra-epithelial lesion**.

Clinical presentation
CIN is asymptomatic.

CIN lesions are characterized by the appearance of white patches on the cervix following application of acetic acid. Distinct vascular patterns can be seen on colposcopic examination of the cervix in high grade CIN. Lesions occur on the anterior lip twice as commonly as the posterior lip. They are found in the transformation zone and areas of squamous metaplasia in the endocervix and stop abruptly at the junction with the native portio squamous epithelium but can extend along the entire endocervical canal. In general, the portion of CIN on the portio surface is low grade (CIN 1) whereas the portion that extends into the endocervical canal is high grade (CIN 2 and 3).
CIN may regress (spontaneously, especially CIN1), persist or progress. If untreated, up to 16% of CIN1 will progress to CIN3 and up to 70% of CIN3 will progress to invasive squamous cell carcinoma in 1 to 20 years. It is not presently possible to predict which lesions will progress. However, the risk of progression to invasive cancer increases and the time required is shorter with increasing severity of the lesion.

Screening
The aim of screening is to prevent the development of cancer. For screening to be effective, a disease should satisfy the following criteria:

- Be common, serious and an important public health concern for the individual and the community.
- The disease condition must have a long, latent interval in which pre-malignant change or occult cancer can be detected for the case of cancer of the cervix it is 10-15years.
- The natural history of the disease, especially, its evolution from latency to disease should be adequately documented.
- There should be effective treatment for pre-malignant change or condition.

Cervical cancer screening satisfies the above criteria, especially with regards to developing countries where it really is a public health problem. Cervical screening has been shown to be effective in several countries. Cervical cancer prevention efforts worldwide have focused on screening women at risk of the disease using Pap smears. Treating precancerous lesions has also prevents cervical cancer in many of the developed countries. In view of the afore mentioned cancer of the cervix is almost extinct in the developed nations, making it the 11^{th} cancer in women and 2^{nd} commonest in developing nations.

Pap smear
The Pap test was developed by Dr George Papanicolaou an American anatomist in 1944. Pap test is used primarily as a tool for screening healthy women for preinvasive cervical cancer (CIN) and early invasive cancer.In as much as pap test is a screening tool,it could also be use to identify women at risk of cervical cancer. Women with early invasive cancer (FIGO Stage 1) are often unaware that they are harbouring the tumour as they are usually symptom free. Diagnosis and treatment of invasive cancer while it is still in the early stages of development signficantly improves the prognosis (chances of long term survival) of the patient. It has been proven over time that the cervical smear may be negative even in the presence of an advanced invasive cervical cancer. This is because blood, inflammatory cells and necrotic debris from the cancer site frequently obscure the abnormal cells in the smear.
The sample for pap smear can be collected in two ways:
a) liquid-based cytology (LBC) - using a cervix-brush a device which samples both endo and ectocervix. These can be used for preparing conventional smear. Some devices have been modified for the preparation of liquid based cytology (LBC) specimens
b) Papanicolaou (Pap) smear test uses a brush or the Ayres spatula to sample the ectocervix. Scraping the ectocervix is performed with a modified spatula (the Ayre spatula or a variation of it), a cyto-brush is used to sample the endocervix. This is the most widely used method in developing countries and some part of Europe for obtaining material for preparing conventional cervical smears.
Pap-smear report may be delivered according to WHO classification, or Bethesda classification, which includes:
Atypical Squamous Cells of undetermined significance (ASC-US)
Low grade Squamous intraepithelia neoplasia(LSIL)
High grade Squamous intraepithelial neoplasia(HSIL)

HPV	Mild dysplasia	Moderate dysplasia	Severe dysplasia	Carcinoma in situ	Invasive cancer
HPV	CIN I	CIN II	CIN III		Invasive cancer
Low grade SIL LGSIL		High grade SIL HGSIL			Invasive cancer

Management

Management of borderline nuclear change

The smear should be repeated at 6 months, interval for 1year and 12 months later. – If all are negative, normal recall can be resumed. If in the course of the follow up, there are a maximum of 3 reports of borderline nuclear change in the follow-up period, referral for colposcopy is advised. At any point in time One report of borderline glandular cells requires immediate referral for further evaluation. In difficult cases, where there is concern that high grade disease may be present, immediate referral can be recommended.

CIN I/Low sil management

CIN I/Low SIL correlates to Nucleus occupying up to 1/2 of the area of the cell (Nucleocytoplasmic ratio of half).

It is advisable that she should have a colposcopy done, in centres where this facilities are not available, "it remains acceptable to recommend a repeat test". If the repeat smear is the same diagnosis (mild dyskaryosis) then a referral must be advised.

CINII/High SIL

CIN II/High SIL correlates to Nucleus occupying up to ½ to 2/3 of the area of the cell(Nucleocytoplasmic ratio of ½ to 2/3).

All patients with moderate dyskaryosis should be referred for colposcopy.

CIN III/ High SIL

CIN III/High SIL correlates to Nucleus occupying more than 2/3 of the area of the cell (Nucleocytoplasmic ratio greater than 2/3). The nucleus may have a bizarre shape.

Referral for colposcopy is the standard approach of management.This will include tissue biopsy for histology.

Invasive squamous carcinoma

The histological features are essentially that of Bizarre nuclear changes and keratinisation.

In this case an URGENT referral for colposcopy and tissue diagnosis is advised.

Treatment

Low grade lesions

In the treatment of this disease entity a colposcopy, with or without a repeat smear, and or tissue biopsy is an essential requirement as stated above. The uses of additional investigative tools are very essential in the treatment of this condition. The time interval between diagnosis and treatment can be very crucial.

The option of treatment range between Cryotherapy, cold coagulation, Laser agglutination therapy and Electrocautery. A lot of caution must be applied to avert over treatment especially in young women who are still desirous of conception (over treatment can cause fertility problems).

The follow up schedule as stated above and the patient should be encouraged to adhere to this to achieve the desired goal of screening.

High grade lesions

The additional investigations include Colposcopy, repeat smear and tissue biopsy is important toward establishing a diagnosis,because the treatment involved is usually irreversible. Such definitive treatment includes ablative procedures and amputation surgeries.

The definitive treatments include Cold coagulation, Lletz, laser agglutination therapy, electrcautery, knife cone biopsy and trachelectomy.

Follow up of patients on treatment

The Follow-up of women who have been treated for CIN is very crucial to ensure that there is no progression of the disease condition.

- CIN1 – repeat smears at 6months, 12months and 2years this is the schedule if the smear is persistently negative.
- CIN2 and above –This categories of patients require annual smears for 10 years of follow up.
- CGIN (Cervical Glandular Intraepithelia Neoplasia) – are at greater risk of recurrent disease so they are recommended to have smears every 6months for 2years, then annually for 10 years

Follow-up of women with low grade smears but normal colposcopy and no biopsy – require a repeat smear at 6 months, 6 months, 12 months, then return to normal recall

Follow-up of women after hysterectomy for CIN or SCC :

Where there was complete excision and the margins were clear of dysplastic cells, vault smears should be carried out at 6 months and 18 months before recall can be cancelled as no further smears are required.

In the case of women with incomplete or uncertain excision at hysterectomy, they would require follow-up as for women with CIN2 or above.

In women who have been exposed to radiotherapy as an adjuvant therapy, Smears are not advised in this group of women.

HPV vaccination and cervical intra-epithelia neoplasia

In a randomised control study (double blinded) it was concluded that, In young women who have not been previously infected with human papillomavirus-16 (HPV16), vaccination prevents HPV16-related cervical intra-epithelial neoplasia (CIN). It should be noted that only 75% of all cervical cancers are caused the HPV viruses 16 and 18, it is therefore still possible for a woman to develop cervical cancer even though they are immunised. This is because there are other sero types of HPV not covered by those vaccine in the market.

5. Materials of student activization during lecture:

Questions:

1. Specifics of anamnesis gathering in gynecological patients?
2. What special examination methods in gynecology do you know?
3. What is colposcopy and how is it performed?
4. What epithelium are endocervix and ectocervix covered by?
5. Can there be asymptomatic fibroids?
6. What does it mean, a functional cyst of ovary?
7. What contraindications to surgical treatment of ovarian tumors do you know?

6. General material and methodical facilities of lecture:

Study classroom: lecture auditorium
Facilities: auditorial
Equipment: multimedia projector, screen
Illustrative material: slides, tables

LIST OF RECOMMENDED STUDY LITERATURE IN OBSTETRICS AND GYNECOLOGY

Main

1. Gynecology (edit by I.B. Ventskivska).- K.: Medicine,2010.-160 p.
2. D C Dutta's textbook of gynecology, 6th edition. Hiralal Konar. – 2013. – 686 p.

Additional

1. Cervical cancer. WHO guidelines. – 2014.
2. CIN and cervical cancer. Clinical guidelines, 2014. Ministry of Health of Ukraine.