Objectives

- Discuss pap smear reporting
- Describe the Bethesda system 2006
- Discuss management of unsatisfactory smears and smears with no T zone component

Cervical Cancer

- Pap smear screening resulted in dramatic reduction in cervical cancer
- The value of accurate screening can be reduced by loss to follow-up or undertreatment of significant lesions

Pap Smear Reporting

- Pap system of reporting
  - Bethesda 1988 system
  - Bethesda 1991 system
  - Bethesda 2001 system
  - Bethesda 2006 system

Faculty

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Emory University Regional Training Center
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<table>
<thead>
<tr>
<th>Pap Reporting</th>
<th>WHO Reporting</th>
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<tbody>
<tr>
<td>• Class 1</td>
<td>• CIN 1</td>
</tr>
<tr>
<td>– Normal</td>
<td>– Mild dysplasia</td>
</tr>
<tr>
<td>• Class 2</td>
<td>• CIN 2</td>
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<tr>
<td>– Atypia, inflammation, reactive change</td>
<td>– Moderate dysplasia</td>
</tr>
<tr>
<td>• Class 3</td>
<td>• CIN 3</td>
</tr>
<tr>
<td>– Dysplasia</td>
<td>– Severe dysplasia</td>
</tr>
<tr>
<td>• Mild, moderate and severe</td>
<td>– Carcinoma in situ</td>
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<tr>
<td>• Class 4</td>
<td></td>
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<tr>
<td>– Carcinoma in situ</td>
<td></td>
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<tr>
<td>• Class 5</td>
<td></td>
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<tr>
<td>– Invasive cancer</td>
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<table>
<thead>
<tr>
<th>Bethesda System</th>
<th>Bethesda 2006</th>
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<tbody>
<tr>
<td>• Bethesda 1988</td>
<td>• 146 experts</td>
</tr>
<tr>
<td>• Bethesda 2001</td>
<td>• 29 organizations</td>
</tr>
<tr>
<td>• Bethesda 2006</td>
<td>• Met September 18-19, 2006 in Bethesda, MD</td>
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<tr>
<td></td>
<td>• Developed revised, evidence based consensus guidelines for management of abnormal pap smears</td>
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<tr>
<th>Bethesda 2006</th>
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<tr>
<td>• ASCUS</td>
<td>Recommendations for HSIL and AGC underwent only minor changes</td>
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<tr>
<td>• LGSIL</td>
<td></td>
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<tr>
<td>– Management unchanged for the above 2 categories except for adolescents</td>
<td>More emphasis placed on immediate screen and treat for HSIL lesions</td>
</tr>
<tr>
<td>– Cytologic follow-up for 2 years approved for adolescents</td>
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Bethesda 2006

- HPV testing was incorporated into the management of AGC after initial evaluation with colposcopy and endometrial sampling

Bethesda 2006

- The 2004 interim guidance for HPV testing as a adjunct to cervical cytology for screening in women 30 years of age or older was formally approved

Adequate Specimen

- Conventional Smear:
  - 8,000-12,000 well visualized cells should be seen
- Liquid-based Pap:
  - 5,000 well visualized cells should be seen
  - Epithelial cells may be obscured by inflammation
  - If >75% of cells are obscured, it is considered unsatisfactory

Adequacy of Specimen

- Satisfactory specimen contains
  - 10 well preserved endocervical cells or
  - 10 squamous metaplastic cells

Transformation Zone Not Present

- If Pap is otherwise normal, no higher risk of subsequent detection of high grade SIL
- Most women without an endocervical or transformation zone component can be re-screened in 12 months

No T Zone Components

- Repeat testing is recommended for women at higher risk of neoplasia such as:
  - Immunocompromised
  - HPV +
  - previous abnormal pap smears
  - Inability to visualize the cervix
  - Insufficient previous screening
Unsatisfactory Pap Smears
- Pap smears that are unsatisfactory need to be repeated in 2-4 months
- If three consecutive specimens are unsatisfactory, colposcopy is recommended
  - Histologic abnormalities were found in 16% of this population

Abnormal Pap Smears
- 50-60 million pap tests per year in US
- 3.5 million are classified as abnormal and require some form of medical follow-up
- 10,000 new cases of cervical cancer seen each year in the US
- 4,000 deaths from cervical cancer

Abnormal Pap and Cervical Cancer
- Determining which women with abnormal Pap tests are at risk of significant cervical disease and treating them presents a:
  - major public health challenge
  - multibillion dollar cost to our healthcare system

Inconclusive Pap Smears
- Almost 2 million Pap smears each year are classified as “inconclusive”
  - ASC-US, ASC-H and LSIL
- Most of them have no detectable problem
- Less than one fifth of these women have a significant precancerous lesion

Inconclusive Pap Smears
- Although these changes are mild, they may result in:
  - Anxiety
  - Unnecessary medical procedures
  - Extra costs to healthcare system

Abnormal Pap Smears
- Effective cervical cancer prevention requires
  - Recognition and treatment of the precursors of invasive cancer
- The 2001 Bethesda System of nomenclature describes the categories of epithelial cell abnormalities seen on pap smears
## 2001 Bethesda System

- **Squamous Cell:**
  - Atypical Squamous Cells
    - ASC-US (undetermined significance)
    - ASC-H (can not exclude HSIL)
  - Low-grade squamous intraepithelial lesions
    - Mild dysplasia
    - HPV changes

- **Squamous Cell:**
  - High-grade squamous intraepithelial lesions
  - Moderate and severe dysplasia and carcinoma-in-situ (CIN II and CIN III)
  - Squamous cell carcinoma

## 2001 Bethesda System

- **Glandular Cell:**
  - Atypical glandular cells (AGC)
    - Endocervical
    - Endometrial
    - Not otherwise specified (NOS)

- **Glandular Cell:**
  - Atypical glandular cells
    - Favor neoplasia
    - Specify endocervical
    - Not otherwise specified (NOS)
  - Endocervical adnocarcinoma in situ (AIS)
  - Adenocarcinoma

## Precancerous Precursors

- CIN 2, CIN 3, adeno-carcinoma in situ (AIS) are collectively referred to as CIN2/3+

- Cancer precursors include:
  - CIN 3, AIS and to a lesser extent CIN 2

## HPV and Abnormal Paps

- The presence of HPV is a marker for the risk of diagnosis of CIN2/3+

- Only 1 in 10 to 1 in 30 HPV infections are associated with abnormal cervical cytology

- Even a smaller proportion are associated with CIN2/3+
HPV

- Among women with negative cytology and a positive HPV test result, only 15% will have abnormal cytology results within 5 years

CIN Regression

- Regression for CIN
  - 60% for CIN 1 and 40% for CIN 2

CIN 1

- CIN 1 is the histologic appearance of cells producing HPV
- The goals of cervical cancer screening:
  - Not to prevent CIN
  - But to prevent and treat
    - Early invasive cervical cancer
    - Reduce mortality

Management of Abnormal Pap

- Atypical Squamous Cells:
  - The risk of cancer and CIN 2/3+ is low
    - 0.1-0.2% for cancer
    - 6.4-11.9% for CIN2/3+

Atypical Squamous Cells

- Options include:
  - Immediate colposcopy
    - Provides rapid diagnosis but expensive
  - HPV DNA testing triage
  - Repeat cytology at 6 and 12 months
<table>
<thead>
<tr>
<th>HPV Testing</th>
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<tr>
<td>- Hybrid Capture DNA 2 assay for 13 oncogenic HPBV sub types</td>
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<td>- Performed on the liquid based pap specimen</td>
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<td>- Usually done within 3 weeks of obtaining the specimen</td>
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<th>ASCUS (HPV+) in Adolescents</th>
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<tr>
<td>- The risk of invasive cancer approaches zero in adolescents</td>
</tr>
<tr>
<td>- HPV infections are common and self limiting in adolescents</td>
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<tr>
<td>- Colposcopic evaluation is not necessary</td>
</tr>
<tr>
<td>- Can be monitored with pap smears at 6 and 12 months</td>
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<tr>
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<tr>
<td>- Recommendations are similar for ASC and LSIL in adolescent girls</td>
</tr>
<tr>
<td>- LSIL represents HPV infection and most adolescents clear HPV and LSIL</td>
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<tr>
<td>- Follow-up Pap at 6 and 12 months is adequate</td>
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<table>
<thead>
<tr>
<th>ASCUS and LSIL in Adolescents</th>
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<tr>
<td>- Follow-up with cytology or HPV for up to 2 years is reasonable according to Bethesda 2006 guidelines</td>
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<tr>
<td>- More frequent in younger populations with larger number of recent partners</td>
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<td>- Represents the appearance of cells that are actively engaged in HPV replication</td>
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<td>- HPV testing is of limited value</td>
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<tr>
<td>- The risk of CIN 2/3+ at initial colposcopy following an LSIL is between 15% and 30%</td>
</tr>
<tr>
<td>- Colposcopy is recommended for these women</td>
</tr>
<tr>
<td>- For adolescents with LSIL, follow-up with Pap at 6 and 12 months is reasonable</td>
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</table>
### LSIL in Adolescents

- Follow-up at 6 and 12 months
  - Those with HSIL need colposcopy
- Follow-up at 24 months
  - Those with ASCUS or greater need colposcopy
  - Bethesda 2006 guidelines

### LSIL in Postmenopausal Women

- Options include:
  - Reflex HPV DNA testing
  - Repeat cytology at 6 and 12 months
  - Colposcopy
  - 2006 Bethesda guidelines

### ASC-H

- Atypical squamous cells-cannot exclude HSIL (ASC-H);
  - Includes 5-10% of ASC Pap smears
  - CIN2/3+ seen in 24-94% of such cases
  - Immediate colposcopic intervention is necessary
  - HPV testing is not cost effective

### HSIL

- Among women with HSIL cytology results:
  - CIN 2 and CIN 3 have been reported in 70% or more cases
  - Invasive cancer is seen in 1-2% of cases
  - Colposcopy with endocervical evaluation should be done
  - Entire vagina should be examined
  - See and treat approach can be followed if lesion seen

### AGC

- Atypical Glandular Cells:
  - Histological correlation:
    - 9-38% of women with AGC have significant neoplasia
    - 3-17% have cancer
    - CIN is the most common lesion associated with AGC

### AGC

- Source of the lesion:
  - Cervix
  - Endocervix
  - Endometrium
AGC

- Evaluation includes:
  - Colposcopy
  - Endocervical curettage
  - Endometrial sampling
    - With abnormal endometrial cells
    - Women >35 years of age
    - Younger women with abnormal bleeding, morbid obesity and oligomenorrhea

- When evaluation is negative and histology is negative, follow-up includes:
  - AGC favor neoplasia: excision is warranted
    - Cold knife cone is a good choice
  - AGC and AGC NOS
    - Pap and ECC every 6 months until 4 consecutive negative smears are obtained

How Should CIN 1 Be Managed?

- Depends on the preferences of the
  - Physician and the patient
  - For most young women, observation seems appropriate
  - Follow-up with pap smear every 6 months X 2
    - Colposcopy for an ASC or higher
    - or a positive HPV at 12 months

- CIN 2 and 3 are recognized potential cancer precursors
  - Although CIN2 is associated with significant spontaneous regression
    - 40% of CIN 2 cases regress over 2 years
  - Immediate treatment of CIN2 and CIN 3 with excision or ablation is recommended in non-pregnant patients

CIN 2 in Adolescents

- Care of the adolescent with CIN 2 may be individualized
- Treatment may be deferred
- Close follow-up with pap and colposcopy may be adequate

Management of AIS

- Cold-knife conization is recommended
  - To preserve specimen orientation
  - Permit optimal interpretation of histology and margin status
- LEEP is not recommended
Hysterectomy for CIN 2/3+
- Hysterectomy is not the initial treatment of choice for
  - CIN 2 or 3
  - May be considered for persistent or recurrent CIN 2 or 3

Abnormal Pap in Pregnancy
- ASC or LSIL:
  - Colposcopy during pregnancy or at 6-12 weeks postpartum
- ASC-H
  - Immediate colposcopy

Abnormal Pap in Pregnancy
- HSIL
  - Immediate colposcopy
- AGC
  - Immediate colposcopy
  - No endocervical sampling is done during pregnancy

Pregnancy
- CIN is not treated in pregnancy
- Excision should be considered
  - If lesion is suspicious for invasive CA
- Repeat colposcopic evaluation is done during pregnancy as needed
- Reassessment by colposcopy
  - 6-12 weeks postpartum

Treatment Modalities for CIN
- Cryotherapy
- Laser ablation
- LEEP
- Cold knife cone biopsy
  - Cryotherapy or laser ablation are done only when endocervical pathology is ruled out

See and Treat Approach
- During colposcopic evaluation, when significant abnormality is found, LEEP is performed to both evaluate and treat the precancerous condition
Management of Cervical Disease

- Diagnostic Procedures:
  - HPV DNA testing
  - Colposcopy
  - LEEP (both diagnostic and therapeutic)
  - Cone biopsy (both diagnostic and therapeutic)

Hybrid Capture DNA Assay

- Hybrid Capture DNA 2 assay
- Designed to detect 13 high-risk HPV subtypes
  (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)

HPV DNA (High Risk) Testing

- Potential indications:
  - Triage of patients with ASCUS
  - Surveillance of HSIL
  - Combination Pap/DNA testing

Self Collected HPV DNA

- Studies suggest that self-collected specimens for HPV testing may offer
  - A means to increase screening
  - Primary screening of older women

Founier Self Collection Device

Colposcopy

- Evaluation of the
  - Cervix and vagina
  - Vulva
- With 10 – 25 times magnification
- Acetic acid 3-6 % solution used
- Cervix and vagina are evaluated before and after acetic acid is applied
Colposcopy

- Pap smear is a screening test
- Colposcopy is the diagnostic test to confirm the disease process

Colposcopy

- Colposcopy is performed when:
  - The pap smear is abnormal
  - The cervix looks abnormal
  - Women are exposed to DES in utero

Treatment

- Cryotherapy
- Laser
- Cone biopsy
- LEEP (Loop Electrical Excision Procedure)

Treatment of Cervical Disease

- Treatment of the precancerous disease depends on the
  - Severity of the disease
    - Mild, moderate or severe dysplasia or CIS
    - Involvement of the endocervical canal
    - On the age of the patient such as an adolescent

Cryotherapy

- Destruction of abnormal tissue by freezing
- Cryotherapy destroys normal tissue along with the abnormal tissue
Cone Biopsy

- Cone biopsy is an extensive form of cervical biopsy
- A wedge shaped tissue is removed from the cervix and examined under a microscope

Cone Biopsy

- Cone biopsy removes abnormal tissue that is high in the cervical canal
- A small amount of normal tissue around the abnormal tissue is removed so that a margin free of abnormal cell is left in the cervix

Cold Knife Cone Biopsy
Cone Biopsy

- Cone biopsy can be done using
  - A surgical knife (cold knife cone)
  - A carbon dioxide laser
  - LEEP (Loop Electrical Excision Procedure)

LEEP/LLETZ

- Loop Electro-surgical Excision Procedure, also known as large loop excision of the transformation zone is a technique used for treatment and diagnosis of cervical dysplasia.
LEEP

- Performed as an outpatient technique at the gynecologist’s office except under special circumstances
- The cervix is numbed, and a portion of the cervix is removed with a thin wire loop carrying a small electrical current
- The tissue is then sent for pathologic evaluation

Counseling

- Emphasize practicing safer sex in the future
- Encourage involvement of partners in the discussion
- Provide culturally sensitive and appropriate educational materials that are helpful
- Give them opportunity to return and discuss the information at a later time

Cervical Cancer

- HPV is the primary cause of cervical cancer
- In most cases, the HPV is harmless and causes no symptoms
- The majority of women with HPV will not develop cervical cancer
- Cervical cancer is completely preventable if precancerous changes are detected and removed from the cervix

References

- The HPV DNA virus hybrid capture assay:
- What is it-and where do we go from here? www.mlo-online.com (March 2003)
References

- Bethesda 2006 guidelines