Abnormal Pap Smear

See also CIN
See also Pap Smear
See also HPV

Background

1. Definition
    - Abnormal results:
        - ASC (Atypical Squamous Cells)
        - ASC-US (Atypical Squamous Cells of Undetermined Significance)
        - LSIL-CIN 1 (Low Grade Squamous Intraepithelial Lesion- Cervical Intraepithelial Lesion)
        - High-Risk HPV(+)
        - HSIL-CIN 2-3 & CIS (High Grade Squamous Intraepithelial Lesion Cervical Intraepithelial Lesion 2-3 and Carcinoma In Situ)
        - AGUS (Atypical Glandular Cells of Undetermined Significance)
        - AIS (Adenocarcinoma in Situ)
        - Invasive SCC (Invasive Squamous Cell Cancer) or AdenoCA (Adenocarcinoma)
          (see CIN)

Pathophysiology

1. Pathology
    - Begins by primary infection of cervical squamous epithelium proliferating basal cells by high risk HPV
        - Types 16,18,45,31,33,52,58 and 35
    - HPV 6 and 11
        - 25% of all CIN 1 and 90% of all anogenital condyloma
    - HPV 16,18,31,33 and 45
        - 63 to 97% of invasive cervical cancers
    - CIN 1: Acute low grade histologic manifestation of high risk HPV
    - CIN 2 and CIN 3: cervical cancer precursors
    - Infection w/ high risk HPV type → Immune system activation to control and clear infection, presence of some co-factors such as smoking → persistent HPV infection → viral genome incorporated into host cell genome → inactivation of p53 tumor suppressor gene and retinoblastoma gene by the viral genome → immortalization of the infected cells → absent effective immune surveillance by the host → malignant transformation
    - LSIL most likely the initial infective and potentially progressive state → may be controlled by host immune system → disappear w/o intervention
    - In majority of individuals
        - 70% of new infections resolve w/in 1 yr
        - 90% resolve w/in 2 yrs
    - In susceptible women and under certain conditions, cervical cancer can develop approximately 12-15 yrs after the initial infection

- Persistence of HPV for periods >6 mos
    - Related to older age
    - Presence of a high risk HPV
    - Infection w/ multiple HPV types
- Squamous cell carcinomas most commonly occurring form of cervical cancer and develop from CIN 1, LSIL
    - Current hypothesis: HSIL or CIN 2/3 lesions may develop w/in 2-3 yrs of persistent HPV infection in susceptible individuals
- Once HSIL develops → viral oncogenes E6 and E7 abrogate cell cycle control and apoptosis mechanisms → signals transition from viral infection to malignant process → loss of tumor suppressor genes and changes in growth modulating influences → progression from CIN 2/3 lesions to overt malignancy
- See CIN Pathology

2. Prevalence
    - Similar in pregnant and non-preg women
    - 6.2 million new infections occur annually in individuals 14-44 yrs
    - In general population in asymptomatic women → 2-44%
    - Incr each yr b/n ages 14-24 yrs, declines through age 59
    - Highest genital HPV infection rates:
        - In sexually active women <25 yrs
    - One in every two people will acquire genital HPV infection during their lifetime
        - By the age of 50, this proportion reaches 80% in women
    - Postpartum prevalence
        - Significantly lower
    - Similar rates of ASC-US, LGSIL, HGSIL in preg vs. non-preg pts
3. Incidence
    - 1-15 cases per 10,000 pregnancies
    - Mean age of diagnosis: 34 yo
    - Incidence of each stage at diagnosis:
        - 83% Stage I
        - 10% Stage II
        - 3% Stage III
        - 2% Stage IV
        - Stage for stage: prognosis is similar to that of non-preg pts
4. Risk factors
    - Same as for non-preg women
    - Younger age at first intercourse
    - High lifetime number of sex partners and increased frequency of sexual intercourse
    - Intercourse w/ men whose previous partners had cervical cancer
    - Anal sex
    - Hispanic and African-American ethnicity
    - Others: cigarette smoking, immunodeficiency including HIV, alcohol consumption
    - Dietary and nutritional factors
    - Family hx of cervical cancer

- Hx of chlamydia, trichomonas or herpes simplex virus infection
- Inadequate screening
- Multiparity
- Persistent HPV infection
- Use of oral contraceptive pills

Diagnosis

1. History
    - Early cervical Cancer:
        - Pts usually asymptomatic
    - First sx:
        - Irregular vaginal bleeding
        - Most often postcoital
        - May occur spontaneously between menses
    - Large Cancers:
        - Bleed spontaneously
        - Foul smelling vaginal discharge
        - Pelvic pain
    - More widespread cancer:
        - Obstructive uropathy
        - Back pain
        - Leg swelling
2. Physical exam
    - Note presence of any lesions visible w/o aid of colposcope
    - Findings upon colposcopic inspection
        - Accuracy in pregnancy: 99.5%
    - Complication rate:
        - 0.6% N0 invasive cancer missed
        - 4% required cone biopsy or wedge resection
3. Screening
    - Pap test:
        - Sampling of endocervix and ectocervix
        - Either conventional or liquid based
    - Routine Antenatal care in US:
        - Cervical smear at first prenantal visit
            - To exclude invasive cancer
    - Specimen labeled as satisfactory:
        - Cellularity requirement:
            - At least 8000 squamous cells for conventional smear or 5000 squamous cells for liquid specimen
        - At least 10 squamous metaplastic or 10 endocervical cells
            - Ensures specimen represents elements of transformation zone
            - This area is most vulnerable to neoplastic change
    - Specimen labeled as unsatisfactory:
        - Insufficient cellular material

- MANAGING UNSATISFACTORY PAP TESTS:
  - Pap test lacking endocervical cells, w/ borderline cellularity, or w/ obscuring blood or inflammation
    - Repeat in 6 mos if pt has prior abnormal Pap w/ CIN or glandular abnormality
    - (+) HPV test w/in the past 12 mos
    - No cervical visualization during Pap test
  - If cytology reading on prior Pap obscured for any reason
  - If HPV test performed w/ Pap test and returned negative
    - Repeat Pap may be delayed for additional 12 mos
  - W/ unsatisfactory Pap for other reasons, treat any underlying infections and repeat Pap in 2-4 mos

4. Description and Interpretation of Cytologic Results:
   - Negative for intraepithelial lesion or malignancy: negative, or benign,
   - Pap test result- non-neoplastic findings:
     - Represent reactive cellular changes associated w/ inflammation, infection, or atrophy
   - Common organisms include trichomonas, actinomyces species, and fungal organisms consistent w/ Candida; shift in flora suggestive of bacterial vaginosis
   - Atypical squamous cells of undetermined significance (ASCUS)
   - Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
   - Low-grade squamous intraepithelial lesion (LSIL)
   - High-grade squamous intraepithelial lesion (HSIL)
   - Atypical glandular cells (AGC)
5. Diagnostic criteria
   - CIN 1 (mild dysplasia)
     - Dysplastic cells occupy the lower third of the epithelium
   - CIN 2 (moderate dysplasia)
     - Dysplastic cells occupy up to the middle third of the epithelium
   - CIN 3 (severe dysplasia, carcinoma in situ)
     - Dysplastic cells extend into the upper third and may occupy the full thickness of the epithelium
   - Invasive cancer
     - Dysplastic cells invade basement membrane
   - AIS (adenocarcinoma in situ)
     - Malignant glandular cells present
6. Effects of Pregnancy on Colposcopic Findings:
   - Pregnancy triggers very active squamous metaplasia:
     - Exaggerated acetowhite changes in response to acetic acid
   - Increase vascularity and stromal edema:
     - Decrease acetowhitening but exaggeration of vascular pattern
   - Stromal edema, increased vascularity, stromal hypertrophy:
     - Cause marked enlargement of the cervix
   - Eversion exposes upper extent of lesions (1st or 2nd trimester)
     - Make colposcopy satisfactory more often

        - Grading more difficult than in the non-pregnant pts
    - Decidual changes can be confusing:
        - May have features consistent w/ invasive cancer → yellow coloration, topography changes, atypical appearing vessels
    - Goal of colposcopy in pregnancy
        - R/O Invasive Cancer: this requires BIOPSY if you suspect HSIL or worse;
        - Experienced colposcopists may elect to omit biopsies of low grade appearing lesions, especially if the cervical cytology is low grade (d/t risk of bleeding from hypervascular cervix)
    - After first trimester, colposcopy best performed by skilled, experienced colposcopist
    - Never perform endocervical curettage during pregnancy
        - Risk of inducing abortion

Management

- Preinvasive dz and Microinvasive Cancer of the cervix
    - Not treated during pregnancy
- Only indication for treatment during pregnancy
    - Histologically confirmed frank invasive cancer

1. ASC-US (Atypical Squamous Cells of Undetermined Significance)
    - Pregnant women over age 20, identical to non-pregnant women
    - Exception: acceptable to defer colposcopy until 6-8 wks postpartum (C III)[1]
    - HPV DNA testing
        - Preferred if liquid based cytology or co-collection available
        - HPV (+): manage in same manner as women w/ LSIL:
            - Colposcopy
                - (+)CIN: manage per ASCCP guideline
                - No CIN, HPV unknown: repeat cytology in 12 mos
                - Cytology in 6 and 12 mos or HPV testing in 12 mos
                - ≥ASC or (+)HPV → repeat colposcopy
                - Negative: routine screening
        - HPV (-): repeat cytology in 12 mos OR
        - Repeat Cytology at 6 and 12 mos
            - Both tests negative– routine screening
            - ≥ ASC on either result, colposcopy
    - Note: Endocervical curettage contraindicated during pregnancy (E III)[1]
2. LSIL
    - Colposcopy is preferred for pregnant, non-adolescent women w/ LSIL cytology (B II)[1]
        - Colposcopy:
            - No CIN 2,3
            - Postpartum follow up
        - Colposcopy:
            - (+) CIN 2,3 manage as per ASCCP guideline
    - Deferring the initial colposcopy until at least 6 wks postpartum is acceptable (B III)[1]

- Endocervical curettage is unacceptable in pregnant women (E III)[1]
- In pregnant women w/o cytologic, histologic, or colposcopically suspected CIN 2,3 or cancer at initial colposcopy, postpartum follow-up recommended (B III)[1]
- Additional colposcopic and cytologic examination during pregnancy unnecessary/contraindicated (D III)[1]

3. HSIL
   - Colposcopy recommended for pregnant women w/ HSIL (A II)[1]
   - Colposcopic evaluation of pregnant women w/ HSIL should be conducted by clinicians experienced in evaluation of pregnancy-induced colposcopic changes (B III)[1]
     - Lack of experience can cause abnormalities to be overlooked or misinterpreted
   - Biopsy of lesions suspicious for CIN 2,3 or cancer preferred
     - Biopsy of other lesions acceptable (B III)[1]
   - Endocervical curettage contraindicated in pregnant women (E III)[1]
   - Diagnostic excision contraindicated unless invasive cancer suspected based on the referral cytology, colposcopic appearance, or cervical biopsy (E II)[1]
   - Reevaluation w/ cytology and colposcopy recommended no sooner than 6 wks postpartum for pregnant women w/ HSIL but w/o CIN 2,3 (C III)[1]
   - For pregnant women w/ CIN 2,3, repeat cytology and colposcopy may be performed every 12 wks w/ repeat biopsy if lesion worsens or cytology suggests invasion
   - Treatment contraindicated w/o cancer confirmation d/t elevated risk of complications: hemorrhage and fetal loss
4. AGC
   - Identical to non-pregnant women except endocervical curettage and endometrial biopsy contraindicated (B II)[1]
   - Initial Pap of AGC-NOS
   - No CIN and No Glandular Neoplasia
     - HPV status unknown
       - Repeat cytology at 6 mos interval x 4 times
     - HPV (-) /HPV (+)
       - Repeat cytology and HPV DNA testing @ 12 mos if HPV (-)
       - At 6 mos if HPV (+)
       - $\geq$ ASC or HPV (+) → colposcopy
       - Both tests negative → routine screening
     - CIN but no glandular neoplasia
       - Manage per ASCCP guideline OR
     - Glandular neoplasia irrespective of CIN
       - Manage per ASCCP
   - Initial pap of AGC (favor neoplasia) or AIS
     - No invasive dz
       - Diagnostic excisional procedure
       - Diagnostic excisional procedure should provide intact specimen w/ interpretable margins (B II)[1]

5. CONIZATION in pregnancy
    - Reserved for rare cases where invasive cancer strongly suspected by cytology, histology or colposcopic impression
    - Not performed for unsatisfactory colposcopy, even if high grade lesion, unless invasive cancer suspected; instead, colposcopy repeated at intervals until examination becomes satisfactory (second trimester in most cases)
    - Associated w/ 12% hemorrhagic complications, 5% perinatal mortality, 30% preterm labor rate
6. INVASIVE CANCER
    - Diagnosis: dictates referral to and management in conjunction w/ gynecological oncologist
    - Method of delivery for viable pregnancy:
        - C-section w/ radical hysterectomy
7. POSTPARTUM EVALUATION
    - Likelihood of dz progression during pregnancy small; regression more likely (12-70%)
    - Controversial whether severity of dz diagnosed and route of delivery influence postpartum persistence
    - Reevaluation:
        - 6-8 wks postpartum (to allow healing to occur)
    - Treatment:
        - Based on grade and location of dz identified postpartum

Prevention

1. Same for pregnant and non-pregnant
2. Screening key to preventing development of cervical cancer
3. Sensitivity of conventional pap smear: 51%
4. Specificity: 98%
5. Liquid based pap tests: may miss 15-35% of high grade CIN; sensitivity of 80%
    - Cytology screening programs compensate for low sensitivity by requiring 2-3 annual Pap tests before screening can be performed less frequently
6. Goal of Screening Cervical Cytology: identification and treatment of true cervical cancer precursors
    - CIN 2 and CIN 3:
        - Acceptable as true cervical CA precursors
    - CIN 1:
        - Not considered as true cervical CA precursor; does not need treatment;
            - CONCERN: unrecognized CIN 2, CIN 3 or Cancer

References

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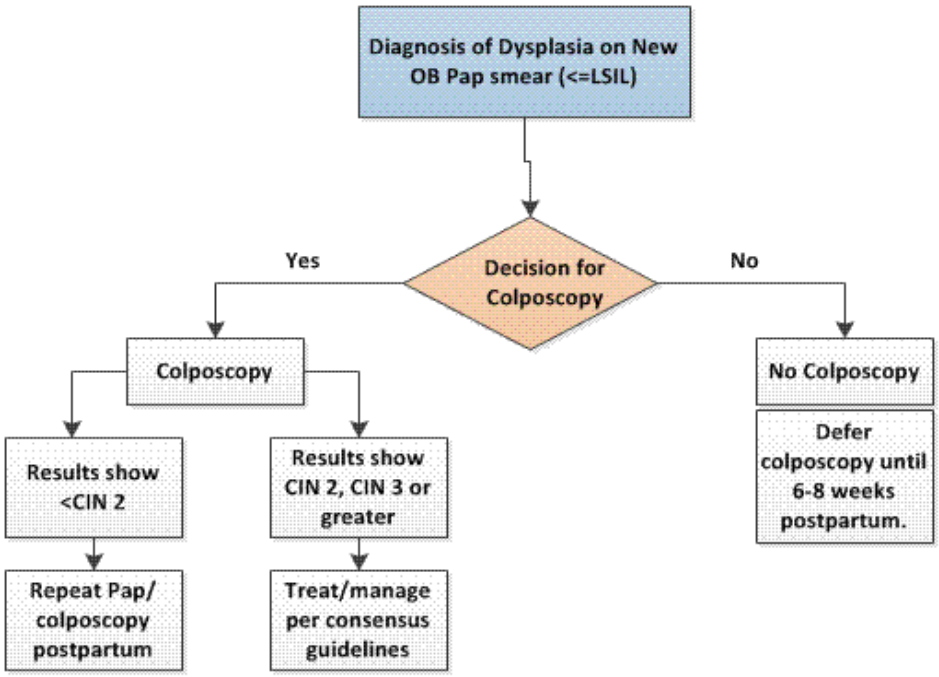

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