HPV IN PREGNANCY

Background

1. Definition: infection with Human papillomavirus (HPV) present during pregnancy
    - HPVs produce epithelial cell tumors of the skin and mucous membranes
    - >100 types of HPV have been identified [1]
2. General Information
    - Classification
        - Latent: asymptomatic infection; detected only with viral DNA testing
        - Subclinical: identified by application of 3-5% acetic acid and inspection
        - Clinical: grossly apparent lesions
    - Typing
        - Low risk: HPV 6 & 11, have low oncogenic potential, more commonly associated with formation of condylomata and low-grade precancerous lesions [1, 5]
        - High risk: HPV 16 & 18. Responsible for most high-grade intraepithelial lesions that can progress to carcinomas [1,2]

Pathophysiology

1. Pathology of Disease
    - Humans only known reservoir for HPV [3]
    - HPV infections transient in majority of individuals
        - 70% resolve in one year; 90% by 2 years [2]
    - Infection begins in proliferating basal cells of squamous epithelium. [2]
    - Infection by high risk HPV types and failure of the immune system to clear the infection, coupled with co-factors such as smoking, lead to persistent infection
    - After time, persistent infection leads to genomic instability and neoplastic transformation of epithelium. [2]
    - Virus can survive for many months at low temperatures without host
2. Incidence, Prevalence
    - Most common sexually transmitted infection (STI) in US [2,3,4]
    - Immunosuppressed patients are at increased risk for developing infections [5]
    - HPV causes virtually all cases of cervical cancer [2,4]
    - Condyloma acuminata most commonly diagnosed viral STI in US
        - Annual incidence is between 500,000 and 1 million [6]
    - Approximately 20 million Americans currently infected with HPV
        - Approximately 6 million new cases annually [6]
    - At least 50% of sexually active men and women are exposed during their lifetime[2]
3. Risk factors [2]
    - Young age (<25 y/o)

- Number and frequency of sexual partners
- Hispanic or African American ethnicity
- Anal sex
- Alcohol consumption and smoking
- Immunosuppression

4. Morbidity/Mortality
    - Women with high grade squamous intraepithelial lesion (HGSIL) or invasive squamous cell cancer (SCC) of the cervix at increased risk for developing cancer in other areas of the anogenital or mucosal tract, including anal or vaginal carcinoma
    - Percentage of cancers caused by HPV infection:
        - Cervical—100% [6,8]
            - Most common malignancy diagnosed during pregnancy (1 in 750) [9]
            - Eight high risk HPV types account for 95% of cervical cancers
                - Types 16 and 18 account for 70% of cervical cancers
        - Anal—90% [8]
        - Vulvar—40% [8]
        - Vaginal—40% [8]
        - Oropharyngeal—12% [8]
        - Oral—3% [8]
    - No evidence that relative immunosuppressive state of pregnancy modifies aggressiveness of HPV[8], although anogenital warts may proliferate in pregnancy[10]
    - Genital warts in pregnancy unlikely to cause any complications [10]
    - Vertical transmission rates
        - HPV infections have low potential of transmitting virus to oral mucosa of infants
        - Time between rupture of membranes and delivery appears to be critical
        - HPV positive infants should be considered contaminated rather than infected, as virus is cleared over several months [11, 12]
    - Most children born with maternal genital warts will not develop complications; rarely, they can develop laryngeal papillomatosis
        - Retrospective cohort from Danish registries between 1974 and 1993 identified 3033 deliveries with maternal warts; of these, 57 respiratory juvenile papillomatosis cases found in ENT records
        - Labor length greater than 10 hours had 3-fold increased risk of disease [13]

Diagnostics

1. History
    - Anogenital Warts

        - Exophytic cauliflower-like lesions typically found near moist surfaces: perianal area, vaginal introitus, vagina, labia, and vulva
        - Smooth warts and keratotic warts
    - Cervical Disease
        - Most lesions subclinical or latent and asymptomatic
        - Genital flat warts are subclinical lesions typically appearing on cervix.
        - If advanced, may report vaginal bleeding/spotting between periods or after sexual intercourse
        - Other symptoms: dyspareunia or fullness in pelvis, pelvic pain, sciatica-like pain, flank pain, chronic anemia, and shortness of breath
    - Anal Cancer
        - Most common: rectal bleeding and sensation of mass
2. Physical Examination
    - Findings on physical exam depend on which tissues involved.
    - Warts: cauliflower appearance, smooth, papular, or keratotic.
    - Cervical flat warts: detected on colposcopic examination with 3-6% acetic acid demonstrating acetowhite changes and abnormal blood vessels that are indicative for HPV-triggered dysplasia
    - Cervical disease: early lesions may appear grossly normal; as disease progresses, cervix may appear abnormal with gross erosions and ulcerations; may extend into vagina
        - Use of colposcopy to detect early neoplasia limited by pregnancy-associated cervical hyperemia, resulting in prominent but normal epithelial changes that may mimic neoplasia [14]
3. Diagnostic Testing
    - Cytologic Testing
        - Cervical cytology utilizing Pap test is standard screening procedure for cervical neoplasia [14]
            - American College of Obstetrics & Gynecology (ACOG) Guidelines: initial pap test at 21 years of age, then every 2 years afterward if the initial screening is negative [14]
            - Interval can be increased to q3 years in women >30 years who are at low risk for cervical dysplasia and with 3 consecutive normal pap tests [14]
    - HPV DNA testing
        - Hybrid Capture II High Risk HPV and the Cervista HPV HR
            - Tests for presence of high risk HPV types (does not identify specific types)

- Preferred method in women age greater than 20 years with Pap test showing Atypical squamous cells of undetermined significance (ASCUS) [14]
- Not recommended in women less than 20 years of age and minimally abnormal cytology tests (ASCUS, Low grade squamous intraepithelial lesions (LSIL)); high prevalence of HPV and spontaneous resolutions rates of 90%, resulting in a very low risk of invasive cancer (SOR:B) [14]
- Also useful in the management of Cervical intraepithelial Neoplasia (CIN) II and III for a test of cure (SOR:C) [14]

▪ Cervista HPV 16/18 testing identifies the presence of HPV 16 or 18
- Useful in women over 30 positive for ASCUS and Cervista HPV HR to specifically identify HPV types 16 and 18

o Procedures
▪ Tissue biopsy
- Can be used to confirm infection if diagnosis uncertain [15]
- Should obtain biopsy of anogenital wart if:
  - Patient immunocompromised
  - Lesion worsens during treatment
  - No response to standard therapy.

▪ Histologic Findings
- Koilocytosis, acanthosis, dyskeratosis, and multinucleation [15]

Differential Diagnosis

1. Benign Lesions
2. Malignant lesions
3. Previous conization of cervix
4. Gynecologic cryosurgery
5. Hemorrhoids
6. Hidradenitis Suppurativa
7. Urethral Warts
8. Vestibular papillomatosis
9. Actinic keratoses
10. Cervical polyp
11. Condyloma lata
12. Dermatitis papillaris
13. Nevi
14. Pityriasis versicolor
15. Nongenital Warts
16. Keloid/Hypertrophic Scar

17. Lichen Planus
18. Psoriasis
19. Seborrheic Keratosis

HPV and Pregnancy

1. Management of genital and cervical papillomas
    - Treatment limited to Tricholoroacetic acid, Cryotherapy, and laser ablation
    - Podophyllin, podophyllotoxin, interferon and 5-FU contraindicated due to potential fetal harm
    - Not enough information on safety of imiquimod or sinecatechins to recommend use in pregnancy [16]
    - Laser treatment in third trimester has lower recurrent rate, but is associated with preterm contraction and preterm labor; causal association unproven. [17]
    - No study done to look at treatment of warts and effect of viral transmission to fetus
    - Due to similar risk of reoccurrence, no single treatment can be recommended over another (SOR:B) [14]
    - In general, treatment may be delayed until postpartum period to assess for spontaneous resolution [10]
    - Cesarean section not proven to prevent HPV transmission
        - Caesarean section may be considered if condyloma obstruct birth canal or could potentially cause hemorrhage and labor dystocia [10]
2. Screening and management of preinvasive disease
    - Management of abnormal screening cervical cytology in pregnancy should follow 2006 Bethesda consensus guidelines [14]
    - Recommended that all pregnant patients undergo Pap test screening at time of initial evaluation; some authors include adolescents age less than 21, due to higher rates of HPV in younger pregnant patients. [18]
        - If normal, follow usual guidelines for follow-up Pap [20]
3. Management of cytologic abnormalities
    - ASCUS
        - Pregnant women >20 years managed the same as nonpregnant women (HPV DNA testing), with exception that colposcopy may be deferred until at least 6 weeks postpartum if indicated [14]
        - Patients HPV negative can be followed with repeat pap test at 6 weeks postpartum [14]
        - Recommend against use of HPV triage in patients < 20 years
            - Risk of cancer is relatively low among pregnant women with ASCUS; some studies have found that antepartum colposcopic evaluation does not help management. [14]

- Atypical Squamous Cells of undetermined significance favor High risk (ASCUS-H)
  - Referral for colposcopy [20]
  - Colposcopy should be performed by physician with experience in evaluating the pregnant cervix [19]
  - Endocervical curettage unacceptable in pregnant women (SOR:B) [14]
  - Although cervical dysplasia commonly regresses, repeat evaluation postpartum essential; persistent high grade disease common [14]
- LGSIL
  - Colposcopy is preferred modality for non-adolescent pregnant woman with LGSIL; deferring procedure until at least 6 weeks postpartum is acceptable [20]
    - For those undergoing colposcopy while pregnant, without evidence of CIN2 or above, postpartum follow-up is recommended [20]
- High Grade squamous intraepithelial lesion (HSIL)
  - Recommend colposcopy [20]
    - Biopsy of lesions suspicious for CIN 2 or higher recommended
      - Diagnostic excision not recommended unless invasive cancer suspected [20] (SOR:A) [14]
    - Lesions < CIN2 should undergo repeat colposcopy at 6 weeks postpartum [20]

4. Management of CIN
   - CIN 1, 2, and 3 have all been associated with low progression rates [23]
   - CIN 1
     - Follow up without treatment [23]
     - Treatment in pregnancy unacceptable (SOR:B) [14]
   - CIN 2,3
     - If no invasive disease and early in pregnancy, may repeat colposcopy and cytological exams at 12 week intervals to detect progression [23]
     - Deferring reevaluation until 6 weeks postpartum acceptable if no suspicion for invasive cancer (SOR:B) [14,23]
     - Excisional biopsy recommended only if invasive disease suspected
     - Only invasive cancer treated [23]
5. Cervical Cancer management
6. No large randomized trials re: care of pregnant patients with cervical cancer.
7. Management based on:
   - Evidence from randomized trials in nonpregnant women,
   - Findings from observational studies of pregnant women, and
   - Unique medical and ethical considerations underlying each individual case

Prevention

1. Two FDA approved HPV vaccines
    - Quadrivalent recombinant HPV vaccine (Gardisil) protects against types 6, 11, 16, and 18
        - Nearly 100% effective in preventing CIN 2 &3 and genital warts in unexposed women
        - 98% effective in preventing high grade precancerous lesions from HPV 16 and 18 in unexposed women [4]
        - No evidence of adverse outcomes in women who became pregnant during phase III vaccine trials. [24]
    - Bivalent HPV vaccine (Cervarix) protects against types 16 and 18
        - 98% effective in preventing high grade precancerous lesions from HPV 16 and 18 in unexposed women
        - Some cross protection for types 31, 33, and 45 [4]
    - Neither vaccine recommended in pregnancy [25]
        - Classified as category B by FDA
        - Completion of series should be delayed until pregnancy completed
        - Lactating women can receive vaccine
2. Limiting new partner encounters
3. Latex condoms provide incomplete protection; HPV can affect areas not covered by condom (however, better than nothing at all) [10]
4. Tobacco use associated with increased risk; smoking cessation may reduce risk of HPV infection [4]

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