Updates in the Management of Complex Atypical Hyperplasia (Endometrial Intraepithelial Neoplasia)

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Professor

Disclosures
• Advisory board/Consultant
  – Clovis
  – AstraZeneca
  – Iovance
• Data monitoring committee
  – Genentech

Objectives
• Review management of endometrial hyperplasia (EH)
• Discuss factors that influence management
• Describe challenges/controversies
  – Classifications
  – Lymph node assessment
Updates in the Management of Complex Atypical Hyperplasia (Endometrial Intraepithelial Neoplasia)

**Definition**
- Proliferation of endometrial glands
  - Gland-to-stroma ratio >50 percent and crowded appearance
  - Varying shapes/sizes and presence of cytologic atypia
- Results from chronic estrogen stimulation

**Incidence**
- Estimated 133 cases/100,000 woman years
  - More common in postmenopausal ages
- Difficult to determine/capture true rates
  - Treatment modalities vary
  - Terminology changes

**Risk factors**
- Increasing age
- Unopposed estrogen therapy
- Obesity
- Early menarche/late menopause (>55 years)
- Nulliparity
- Polycystic ovary syndrome
- Lynch syndrome
- Diabetes
- Estrogen secreting tumor
- Cowden syndrome/family history

Likely mirrors endometrial cancer rates

Same as endometrial cancer
Presentation

- Abnormal/postmenopausal uterine bleeding
- Detection on cervical cytology
  - AGUS
    - Endometrial cells present
- Incidental finding of thickened imaging
  - High risk patient

Diagnosis

- Endometrial sampling is the gold standard
- Office biopsy is acceptable
  - D&C is not necessary
  - May increase detection of unexpected cancer
    - 33% vs 47% rate
- Repeat/additional sampling
  - Insufficient cells
  - High clinical suspicion
  - Persistent or recurrent bleeding within 3-6 months

Terminology

- 1994 WHO classification
  - Hyperplasia with or without atypia
- Simple hyperplasia
- Complex hyperplasia
- Simple hyperplasia with atypia
- Complex hyperplasia with atypia
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Terminology

- Concerns about inter-observer variability
  - 289 specimens of complex atypical hyperplasia underwent blinded review
  - 25% were downgraded to less severe histology
  - 29% were upgraded to cancer
- Only 67% sensitivity for precancerous lesions
  - Goal to identify true pre-malignant conditions that require therapeutic intervention

Terminology

- International Endometrial Collaboration Group
- Computerized morphometric analysis: D-score
  - Prognostic value assigned based on 3 features

<table>
<thead>
<tr>
<th>DPCarrier</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Determined by the relative size of stroma and glands</td>
</tr>
<tr>
<td>Cytology</td>
<td>Determined by architectural complexity and glandular differentiation</td>
</tr>
<tr>
<td>Nuclear abnormalities</td>
<td>Determined by nuclear abnormalities</td>
</tr>
<tr>
<td>Glandular volume</td>
<td>Determined by glandular volume</td>
</tr>
</tbody>
</table>

Benign D<1 and endometrial intraepithelial neoplasia D>1

Terminology: 2014 WHO classification

- Hyperplasia without atypia (non-neoplastic, benign)
  - Changes typically observed with anovulation or other etiology of prolonged exposure to estrogen
  - E.g. Proliferative endometrium or "simple hyperplasia"
- Atypical hyperplasia/Endometrial intraepithelial neoplasm (EIN)
  - Precancerous changes and epithelial crowding displaces stroma
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Diagnosis Considerations

- Risk of progression vs. co-existing cancer

Risk of Progression: Rates

1994 WHO classification

<table>
<thead>
<tr>
<th>Hyperplasia</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>1%</td>
</tr>
<tr>
<td>Complex</td>
<td>3%</td>
</tr>
<tr>
<td>Simple with atypia</td>
<td>8%</td>
</tr>
<tr>
<td>Complex with atypia</td>
<td>23%</td>
</tr>
</tbody>
</table>

Risk of Progression: Rates

- Retrospective cohort of 1443 women with complex or atypical hyperplasia
  - No hysterectomy for at least 8 weeks; followed up to 21 years
  - Rate of progression was 14.9%
  - Three to five fold higher in women not treated with a progestin
- Case control study of 7947 women with hyperplasia
  - Odds of progression (cumulative risk)

<table>
<thead>
<tr>
<th>Hyperplasia</th>
<th>Year 4</th>
<th>Year 9</th>
<th>Year 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonatypical</td>
<td>1.2%</td>
<td>1.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Atypical</td>
<td>6.2%</td>
<td>12.4%</td>
<td>27.5%</td>
</tr>
</tbody>
</table>

- Risk of carcinoma remained elevated for five years or greater [40]
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Risk of Progression: Time

- Population-based study 1
  - Median time to progression 2.5 years (1.01 to 7.9 years) for atypical hyperplasia
  - 5.1 years (1.1 to 11.6 years) among women with complex hyperplasia
  - Excluded cases diagnosed within one year (concomitant carcinoma)
- Population based study 2
  - Median time to progression ~6 years (all hyperplasia)
- Non-population-based study
  - Mean time to progression 4 years (maximum 10 years)
  - Maximum 18 years of follow-up

Coexisting Endometrial Cancer

- 289 hysterectomy specimens for atypical hyperplasia
  - Hysterectomy within 12 weeks
  - 43% with co-existing cancer
    - 18% with less than atypical hyperplasia on biopsy
    - 35% with high risk features
    - 11% had >50% myoinvasion (Stage IB)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>hysterectomy specimens for atypical hyperplasia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>No.</strong></td>
</tr>
<tr>
<td>Hyperplasia grade</td>
<td><strong>Histological grade</strong></td>
</tr>
<tr>
<td>Atypical</td>
<td>5</td>
</tr>
<tr>
<td>Complex</td>
<td>5</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
</tr>
</tbody>
</table>

Coexisting Endometrial Cancer

Trimble, Cancer 2006
Coexisting Endometrial Cancer

• 48% rate of concurrent cancer
• 2 fold risk if stripe thickness ≥ 2 cm

Endometrial Stripe Thickness and Risk of Concurrent Endometrial Cancer


Matsuo, 2015. 36].

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>Age &gt; 60</td>
<td>6.65 (1.75-25.3)</td>
</tr>
<tr>
<td>BMI &gt; 35 kg/m²</td>
<td>2.32 (1.09-4.93)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.51 (1.16-5.39)</td>
</tr>
<tr>
<td>Hyperplasia type (CAH)</td>
<td>9.01 (1.09-74.6)</td>
</tr>
</tbody>
</table>
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Coexisting Endometrial Cancer: Risk factors
- Presence of nuclear atypia
- Normal weight versus morbidly obese
  - Rate of cancer: 45% versus 26%
- Low risk if confined to a polyp
  - Pooled estimate risk of 5.6%
  - In absence of EIN, negative predictive value 100%

Management Options
- Removal of source of unopposed estrogen
- Main management options
  - Surveillance
    - Limited to use in low risk patients
    - E.g. Patient with anovulation, now corrected
    - Resample as indicated
  - Progestin therapy
  - Surgery

Progestin therapy
- Candidates:
  - Fertility preservation
  - Medically unfit for surgery
- Goals of therapy
  - Clearance of disease
  - Normalization of endometrium
  - Prevention of cancer
- Contraindications
  - History of VTE/stroke
  - Severe liver dysfunction
  - Progesterone receptor positive breast cancer
Progestin therapy

- Megestrol acetate
- Medroxyprogesterone
- Norethindrone acetate
- Levonorgestrel intrauterine device
  - Minimal systemic absorption
  - Considered 1st line

<table>
<thead>
<tr>
<th>Hormonal Agent</th>
<th>Dosage and Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megestrol acetate</td>
<td>10-20 mg/d, 5-7 days per month</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>155 mg intramuscularly, every 3 months</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>10-200 mg/d, 3 or 4 cycles, 11-14 days per month</td>
</tr>
<tr>
<td>Levonorgestrel intrauterine system</td>
<td>72 mg in a slow release over 5 years</td>
</tr>
</tbody>
</table>

Trimble, Obstet Gyncol, 2012. ACOG bulletin

Progestin Therapy: Limited data

- Oral contraceptives (estrogen-progestin)
  - Limited studies
- Progestin injections
  - Some data on Depot MPA
  - Typically second line
- Progestin implants
  - Not well studied

Progestin therapy: Response rates

- Meta-analysis of 391 patients with hyperplasia/early stage cancer
  - Variety of progestin therapies
  - 78% response rate
  - 53% complete response (median 39 months follow up)
    - Higher rates in hyperplasia
  - Median time to response: 6 months
  - Recurrence rates of 23-35%
  - Persistent disease in up to 25%
Maintenance therapy

- After regression, progestin maintenance therapy is often appropriate
  - Regimen depends on the following
    - Patient preference
    - Costs
    - Adherence
    - Convenience
    - Side effects
- Options: Levonorgestrel releasing IUD, oral progestin, OCP
- Sources of excess estrogen exposure should be corrected
- Repeat sampling as indicated

Progestin Therapy: Unanswered Issues

- Optimal dose and duration
  - Estimate 12 months
- Appropriate length of follow up after treatment
- Appropriate measures of the clinical and histologic response
- Post-hormonal treatment surveillance
  - May include serial endometrial sampling every 3-6 months

Non standard management options

- Pharmaceutical options
  - Gonadotropin-releasing hormone (GnRH) agonists
  - Aromatase inhibitors
  - Ovulation induction (e.g. clomiphene or aromatase inhibitors)
  - Metformin
  - Danazol
Fertility preservation

- Meta-analysis of pregnancy after progestin therapy
  - 30% (111/370) achieved one or more pregnancies
- Another study reported pregnancy rates
  - 35% in women with cancer
  - 41% in women with hyperplasia
- Pregnancy rates
  - 41% (hyperplasia), 35% (cancer)

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Total Hysterectomy

- Postmenopausal women
- Do not desire future fertility
- High risk of concomitant endometrial cancer
  - Previously discussed risk factors

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Surgical management

- Hysterectomy
  - All surgical routes are acceptable
  - Supra-cervical hysterectomy is inappropriate
  - Morcellation is unacceptable
- Retention of ovaries may be an option
- Endometrial ablation is not acceptable
Lymph node assessment

- Mayo criteria: Intraoperative evaluation
  - Grade 1-2 endometrioid histology
  - Inner 50% invasion
  - Tumor < 2 cm

- Staging
  - Prognostic information
  - Informs adjuvant therapy

- Lymph node assessment
  - Palpation
    - 72% sensitivity
    - Limited to open approach
  - Pre-operative imaging
    - False negative rate
    - Cost-prohibitive

Sentinel Lymph Nodes

Non standard management options

- Alternative surgical treatments
  - Hysteroscopic resection
  - Bariatric surgery
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Sentinel Lymph Node Assessment

- Disadvantages
  - Information does not often change management
  - Unnecessary surgery/overtreatment
  - Risk of complications

- Advantages
  - Eliminate need for second surgery if malignancy on final pathology
  - Alternative to all or none approach
  - Used in DCIS
  - Minimal risks

Sentinel Lymph Node Assessment

- Inadequate surgery versus unnecessary procedure
- Consider stratifying evaluation based on risk assessment

Best approach is a shared decision-making approach

Conclusions

- CAH/EIN is a premalignant lesion
  - Coexisting cancer rates of 40%
  - Cancer progression 27%
- Management options
  - Medical management
  - Hysterectomy +/- lymph node assessment
- Correct the underlying source of unopposed of estrogen
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Thank You
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