Management of Endometrial Hyperplasia

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I have nothing to disclose.

Female Malignancies in the United States

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>Breast</td>
<td>231,840</td>
<td>40,290</td>
</tr>
<tr>
<td>Lung/Bronchus</td>
<td>105,590</td>
<td>71,660</td>
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<tr>
<td>Colorectal</td>
<td>69,090</td>
<td>23,800</td>
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<tr>
<td>Uterine Corpus</td>
<td>54,870</td>
<td>10,170</td>
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<tr>
<td>Ovary</td>
<td>21,290</td>
<td>14,180</td>
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<tr>
<td>Cervix</td>
<td>12,900</td>
<td>4,100</td>
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<tr>
<td>Vulva</td>
<td>5,150</td>
<td>1,080</td>
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</tbody>
</table>

2015 American Cancer Society

Uterine Cancer

- Increase in deaths from 3,000 in 1988 to more than 10,000 in 2015
- 2.6% lifetime risk
- 25% premenopausal\(^1\)
  - 2.5%-14% younger than 40
- 80% low grade endometrioid histology
  - Unopposed estrogen major risk factor

\(^1\) Gadducci A et al., Gynecol Endocrinol 2009
Factors Associated with Hyperplasia & Cancer

![Diagram showing obesity, endometrial hyperplasia, and cancer relationships](image)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>3—10x</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2x</td>
</tr>
<tr>
<td>Late menopause</td>
<td>2.4x</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.8x</td>
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<tr>
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<td>1.5x</td>
</tr>
<tr>
<td>Unopposed estrogen</td>
<td>9.5x</td>
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<tr>
<td>PCOS</td>
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Prognosticators

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<td>PCOS</td>
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Obesity and Health Outcomes

- BMI > 30 with 4-fold increased risk of hyperplasia, and 13-fold if BMI > 40

Weight Loss in Endometrial Cancer and Hyperplasia Patients

- Prospective cohort study of 121 obese women with CAH or early stage endometrial cancer
  - 91% felt acceptable for physician to discuss weight loss and 10% loss of body weight beneficial
    - 35 accepted medical referral
    - 8 accepted referral to bariatric specialist
  - At 3 months
    - Compliance with 16 medical, 1 surgical referral
    - 59% initiated weight loss attempt

References:

1. Gressel GM et al., Int J Gynaecol Obstet 2015
2. Beavis AL et al., Gynecol Oncol Rep 2015
3. Campagnoli C, Gynecol Endocrinol 2013
Natural History of Endometrial Neoplasia

Estimated prevalence as high as 132/100,000

Risk of Progression to Cancer

- Hyperplasia
  - Simple 1%
  - Complex 3%
  - Simple with atypia 8%
  - Complex with atypia 29%

Risk of having concurrent cancer ~30-40%
Do you offer medical or conservative management to patients with hyperplasia before referring to a gynecologic oncologist? For how long?

A. Yes, for 3 months  
B. Yes, for 6 months  
C. Yes, for 9-12 months  
D. No

Do you perform any additional diagnostic work-up prior to offering treatment?

A. Pelvic ultrasound  
B. MRI  
C. Hysteroscopy  
D. D&C  
E. Combination of above

What is your preferred treatment option in endometrial hyperplasia?

A. Provera  
B. Megace  
C. Mirena  
D. Hysteroscopic resection  
E. Combination of above

Predictors of Malignancy

- Multi-institutional cohort study of 813 women with endometrial polyps\(^1\)
  - Older age and history of AUB associated with risk of malignancy
  - Risk estimated to be 0.3-4.8%
- Multicenter study of model predicting presence of carcinoma with CAH\(^2\)
  - Age≥50
  - BMI≥30
  - Menopausal status
  - Endometrial thickness≥12 mm
  - Score≥5 (Higher BMI & thicker endometrium held more weight)

\(^1\)Litta P et al, Gynecol Oncol 2014  
\(^2\)Gungorduk K et al, Gynecol Obstet Invest 2015
Predictors of Concurrent Cancer

- Case control study of 211 with endometrial hyperplasia who underwent hysterectomy\(^1\)
- Predictors of concurrent cancer
  - Age > 60 (OR 6.7)
  - BMI > 35 (OR 2.3)
  - Diabetes mellitus (OR 2.5)
  - CAH (9.0)
- Risk increased with more risk factors identified
  - 7.0% for 1
  - 17.6% for 2
  - 35.8% for 3
  - 45.5% for 4

Screening for Women at High Risk

- 1.5-2x risk if first degree family member with endometrial cancer
- Lynch syndrome (DNA mismatch repair and microsatellite instability) most common mutation
  - 30-70% lifetime risk of endometrial cancer
  - Earlier age of onset than sporadic cases
- Cowden syndrome (PTEN mutation) rare condition leading to 5 fold increase
- BRCA1 associated with 1.9x risk
- Consideration of annual ultrasonography starting at age 35 and biopsy if appropriate

Diagnosis by Ultrasound

- Normal endometrial stripe:
  - Postmenopausal 4-8 mm
  - Postmenopausal on HRT 4-10 mm
- U/S detection of any uterine pathology
  - Sensitivity 85-95%
  - Specificity 60-80%
  - PPV 2-10%
  - NPV 99%

Findings on Pelvic Ultrasound

- Normal endometrial stripe
  - Postmenopausal 4-8 mm
  - Postmenopausal on HRT 4-10 mm
Endometrial Sampling

- Sufficient material obtained in about 90.6% with pipelle
- Diagnostic rates similar with pipelle or curettage in abnormal uterine bleeding (~95%)
- In up to 60% of curettages, less than half endometrium sampled

Ben-Baruch G et al, Gynecol Obstet Invest 1994

Hysteroscopic Assessment in Endometrial Thickening

- Detection of endometrial hyperplasia
  - Sensitivity 76.4%-81%
  - Specificity 76.9%-96%
  - PPV 73.1%-87%
  - NPV 79.1%-93%
- Detection of endometrial cancer
  - Sensitivity 63-83%
  - Specificity 97-99%
  - PPV 77%
  - NPV 95%

Korkmazer E et al, Prz Menopauzalny 2014
Loiacono RM et al, Gynecol Obstet Invest 2015
Gkrozou F et al, Arch Gynecol Obstet 2015

Assessment of Extent of Disease

- 156 women with CAH or grade 1 endometrial cancer who underwent hysterectomy
  - Hysteroscopic directed biopsies higher accuracy than EMB for differentiating hyperplasia from cancer (92% vs 58%)
  - Deep myometrial invasion better assessed by MRI than ultrasound (82% vs 74%, p<0.02)
  - Hysteroscopic biopsies better evaluated cervical involvement than MRI or ultrasound (94% vs 84% and 80%)
  - Combination of MRI and hysteroscopic directed biopsies identified women at highest risk (83%)


Conservative Management in Hyperplasia & Low Grade Cancer

- Society of Gynecologic Oncology recommends imaging be performed to exclude concurrent carcinoma
  - Ultrasound, CT, MRI
  - Confined to corpus, exclude synchronous ovarian tumors or adenopathy
  - MRI more sensitive than ultrasound for evaluation of myometrium but may miss up to 5% of adnexal masses
- Residual hyperplasia at 6 months increases the likelihood of failure of progestin therapy

Grassel GM et al, Int J Gynecol Obstet 2015
**Role of Conservative Management**

- Frequency of surveillance remains under debate
  - Repeat biopsy after 3 months commonly recommended
- Diffusion-weighted imaging-T2 MRI can improve diagnostic performance in predicting deep myometrial invasion in review of 15 studies
  - Age, preoperative tumor grade, and myometrial invasion<50% on MRI not associated with lymph node metastasis
  - Diagnostic accuracy in detecting myometrial involvement significantly lower in premenopausal women (0.42 versus 0.73, p=0.006), but no difference in deep myometrial invasion (0.94 versus 0.95, p=0.99)

**Hormonal Treatment**

<table>
<thead>
<tr>
<th>Type</th>
<th>Dosage/Duration</th>
</tr>
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<tbody>
<tr>
<td>Provera</td>
<td>10-20 mg daily</td>
</tr>
<tr>
<td></td>
<td>12-14 days/month</td>
</tr>
<tr>
<td>Depo Provera</td>
<td>150 mg IM Q3 months</td>
</tr>
<tr>
<td>Micronized vaginal</td>
<td>100-200 mg daily</td>
</tr>
<tr>
<td>Megace</td>
<td>12-14 days/month</td>
</tr>
<tr>
<td>Mirena</td>
<td>40-200 mg daily</td>
</tr>
<tr>
<td></td>
<td>1-5 years</td>
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**Progestins in Non-Atypical Hyperplasia**

- Meta-analysis of 7 randomized trials
  - Mirena achieved significant treatment response
    - 3 months (OR 2.3)
    - 6 months (OR 3.2)
    - 12 months (OR 5.7)
    - 24 months (OR 7.5)
  - Improved response of Mirena compared to oral progestins (OR 2.5)
    - Fewer hysterectomies (OR 0.26)
  - No difference in vaginal bleeding between Mirena and oral progestins

**Type of Progesterone in Hyperplasia**

- Randomized, multicenter trial comparing Mirena to continuous or cyclic Provera
  - 153 women (75% under age 51)
    - 73% with complex hyperplasia
  - Response rates at 6 months
    - 100% Mirena
    - 96% continuous Provera
    - 69% cyclic Provera
  - Side effects
    - 78% irregular bleeding
    - 35% nausea
    - 52% pain
Progestins in Hyperplasia & Cancer

- 34 observational studies with 408 women with early stage endometrial cancer and 151 CAH
  - Endometrial cancer
    - Pooled regression rate of 76.2%
    - Relapse of 40.6%
    - Live birth rate of 28%
  - Complex atypical hyperplasia
    - Pooled regression rate of 85.6%
    - Relapse of 26%
    - Live birth rate of 26.3%
  - IVF resulted in 39.4% live birth rate compared to 14.9% spontaneous conception
  - 1.9% progressed to higher than Stage I cancer, from which 2 died

Oncologic Outcomes with Progestin

- Systematic review of 45 studies of 391 patients
  - Provera (49%), Megace (25%), Mirena (19%), Makena (0.8%)
  - 39 months median follow-up
  - Complete, durable response in 53.2%
    - Higher in hyperplasia than carcinoma (65.8% vs 48.2%)
    - Median time to complete response 6 months
  - Less persistent disease in hyperplasia
    - 14.4% vs 25.4%
  - Recurrence after initial response higher in carcinoma
    - 23.2% vs 35.4%
  - Reproductive outcomes not different between cohorts
    - 41.2% vs 34.8%, p=0.39
    - 117 live births recorded

Regression and Relapse of Hyperplasia with Mirena

- Cohort study of 344 women treated with Mirena or oral progestins for complex hyperplasia
  - Median follow-up 58.8 months (IUD) and 95.1 months (oral)
  - 221 with complex hyperplasia regressed (96.5%) with Mirena
    - BMI>35 associated with failure (32.6% relapsed)
    - 12.7% overall relapsed (only 3.3% with BMI<35)
  - Delivers 20 µg/day of progestin directly to endometrial cavity

Prognostic Factors in Fertility Sparing Treatment

- Chinese women <=40 with CAH or grade 1 endometrial cancer (EC)
  - 32 patients (13 CAH)
    - Mean follow-up 32.5 months
  - Complete response in 84.4%
  - Patients with elevated HgbA1C more likely to experience complete response
    - Decreased effectiveness in patients with PCOS
  - 9 of 21 patients experienced clinical pregnancies
    - 8 with assisted reproductive technology (ART)
Hysteroscopic Resection for Fertility Preservation

- Retrospective study of 23 women up to age 45\(^1\)
  - 3 patients with grade 1 endometrial carcinoma
  - 20 patients with complex atypical hyperplasia
  - Hysteroscopic resection followed by Megace 160 mg/day
- Remission of disease
  - 52.2% after 3 months
  - 39.1% after 6 months
  - 8.7% after 9 months
- 6 underwent second hysteroscopic resection
- 4.3% relapsed at median follow-up of 25 months
- 6 pregnancies with average time of 7.4 months after completion of progestins

Concurrent Carcinoma with Preoperative Hyperplasia Biopsy

- Prospective GOG cohort study of 306 women with preoperative community biopsy of atypical hyperplasia\(^1\)
  - Independent review by 3 gynecologic pathologists
  - Hysterectomy within 12 weeks without interval treatment
- Change in diagnosis
  - 25.6% less than atypical hyperplasia
  - 29.1% diagnosed as endometrial carcinoma
- 42.6% found to have concurrent carcinoma in hysterectomy specimens
  - 30.9% myometrial invasion
  - 10.6% with >50% myometrial invasion

Clinically Significant Outcomes in CAH

- Retrospective review of 150 patients with CAH\(^1\)
  - 36.7% found to have carcinoma at time of hysterectomy
- Change in diagnosis
  - 43.5% with preoperative office biopsy
  - 28.1% with D&C
- Endometrial cancer risk
  - 1.8% grade 3
  - 7.3% lymphovascular space invasion
  - 10.9% deep myometrial invasion
  - 10 patients underwent lymphadenectomy, 1 nodal metastases
- 1.8%-2.1% estimated risk of cancer node involvement with preoperative CAH

Uterine Cancer Staging

- Clinical Stage I will be upstaged 30% of the time at time of primary surgery
  - 9% pelvic nodes
  - 6% para-aortic nodes
  - 5% axilla
  - 12% positive cytology
  - 6% other (e.g. cervical or abdominal disease)
- Clinical Stage II or III will be upstaged 60% of time

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\(^1\)De Marzi P et al, J Minim Invasive Gynecol 2015

\(^1\)Trimble CL et al, Cancer 2006

\(^1\)Costales AB et al, Gynecol Oncol 2015
Surgical Staging

- Hysterectomy, BSO +/- Pelvic/Para-aortic LND
- Risk factors to consider
  - Invasion >50% myometrium
  - High grade, serous, clear cell
  - >2 cm tumor size
  - LVSI (lymphovascular space invasion)
  - Cervical involvement
  - Clinically bulky lymph nodes
- If none of these present, risk of + nodes <10% and survival >90%

Clinical Considerations

- Progestin therapy remains the most tested fertility-sparing option in CAH and early stage endometrial cancer
  - Conservative management should be complemented with referral to an infertility specialist
- Surgical management remains the standard of care for those patients done with childbearing, as up to 40% of patients harbor a co-existing adenocarcinoma and approximately 40% fail treatment

What treatment would you offer patients with hyperplasia who desire fertility?

A. Mirena
B. Cyclic Provera
C. Megace
D. Hysteroscopic resection
E. Still recommend hysterectomy