A 40 year old P0 female reports irregular bleeding. You perform an endometrial biopsy after pelvic ultrasound shows a thickened and irregular endometrium. Final pathology notes endometrial intraepithelial neoplasia or EIN. You recommend:

A. Progesterone therapy
B. Hysteroscopy with D&C
C. Hysterectomy
D. Referral to gynecologic oncologist

A 48 year old P4 obese female with poorly controlled diabetes reports irregular bleeding. Pelvic ultrasound reveals an 11 week size uterus with a fundal fibroid. Endometrial biopsy shows complex hyperplasia. You recommend:

A. Progesterone therapy
B. Hysteroscopy with D&C
C. Hysterectomy
D. Referral to gynecologic oncologist
Female Malignancies in the United States

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>252,710</td>
<td>40,610</td>
</tr>
<tr>
<td>Lung/Bronchus</td>
<td>105,510</td>
<td>71,280</td>
</tr>
<tr>
<td>Colorectal</td>
<td>64,010</td>
<td>23,110</td>
</tr>
<tr>
<td>Uterine Corpus</td>
<td>61,380</td>
<td>10,920</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,290</td>
<td>14,080</td>
</tr>
<tr>
<td>Cervix</td>
<td>12,820</td>
<td>4,210</td>
</tr>
<tr>
<td>Vulva</td>
<td>6,020</td>
<td>1,150</td>
</tr>
</tbody>
</table>

2017 American Cancer Society

Uterine Cancer

- Death rate has increased by 1% per year for whites and 2% for blacks
- 2.6% lifetime risk
- 25% premenopausal
  - 2.5%-14% younger than 40
- 80% low grade endometrioid histology
  - Unopposed estrogen major risk factor

Factors Associated with Hyperplasia & Cancer

- Obesity: 3–10x
- Nulliparity: 2x
- Late menopause: 2.4x
- Diabetes: 2.8x
- Hypertension: 1.5x
- Unopposed estrogen: 9.5x

Prognosticators

- Gadducci A et al, Gynecol Endocrinol 2009
Meta-analysis of 65 articles showed that with abnormal bleeding risk of atypical hyperplasia or cancer 1.31% (higher with inter-menstrual bleeding).\(^1\)

ACOG Committee Opinion #631 (May 2015)

- Endometrial intraepithelial neoplasia (EIN) better encompasses premalignant criteria to more widely used 1994 WHO schema utilizing “atypical hyperplasia”
  - Interobserver reproducibility greater with EIN
- Hysteroscopy with directed dilatation and curettage recommended for evaluation
- Total hysterectomy recommended for definitive management when appropriate
- Systemic progesterone therapy can be used if fertility desired or poor surgical candidate
  - Serial sampling Q3-6 months

Comparing WHO and EIN Systems

- Debate on existence of simple atypical hyperplasia, whereas simple and complex hyperplasia thought to have high likelihood to regress with progesterone
- EIN system proposed in 2000 but not gained widespread acceptance due to cost and lack of experience with computerized D-scoring\(^1\)
  - D-score measures stromal volume as a proportion of total tissue volume (stroma + epithelium + gland lumen)
  - Benign (D >1), indeterminate (0< D <1), or EIN (D <0)
- EIN classification demonstrated moderate interobserver reproducibility and correlates with progression to endometrial carcinoma similar to WHO\(^2\)
- Adequate comparative studies between EIN & WHO lacking

\(^1\)Mutter GL et al, Gynecol Oncol 2007
\(^2\)Lacey JV et al, Cancer 2008
Risk of Progression to Cancer Based on 1994 WHO Classification

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

Risk of having concurrent cancer ~30-40%

2015 WHO Classification

<table>
<thead>
<tr>
<th>Term</th>
<th>Synonym</th>
<th>Genetic Changes</th>
<th>Coexistent Cancer</th>
<th>Progression to Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia without atypia</td>
<td>Simple hyperplasia Complex hyperplasia</td>
<td>Low level somatic changes</td>
<td>&lt;1%</td>
<td>RR 1.01-1.03</td>
</tr>
<tr>
<td>Atypical hyperplasia or EIN</td>
<td>CAH Simple hyperplasia with atypia</td>
<td>MSI PAX2 PTEN KRAS CTNNB1</td>
<td>25-33%</td>
<td>RR 14-45</td>
</tr>
</tbody>
</table>

Concurrent Carcinoma with Preoperative Hyperplasia Biopsy

- Prospective GOG cohort study of 306 women with preoperative community biopsy of atypical hyperplasia
  - 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

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

Trimble CL et al, Cancer 2006

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%

Hysteroscopy in Estimation of Endometrial Cancer

- Systematic review of 27 studies of 1106 patients
- Mean risk of cancer after atypical hyperplasia diagnosed by
  - Curettage 32.7%
  - Hysteroscopic biopsy 45.3%
  - Hysteroscopic resection 5.8%

Ultrasound in Detection of Uterine Pathology

- Sensitivity 85-95%
- Specificity 60-80%
- PPV 2-10%
- NPV 99%

Imaging in Workup and Surveillance

- 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

References:
1. Korkmazer E et al, Prz Menopauzalny 2014
2. Loiacono RM et al, Gynecol Obstet Invest 2015
Role for Conservative Management

- 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\(^1\)
- Residual hyperplasia at 6 months increases the likelihood of failure of progestin therapy\(^2\)

<table>
<thead>
<tr>
<th>Type</th>
<th>Dosage/Duration</th>
</tr>
</thead>
<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></td>
<td>12-14 days/month</td>
</tr>
<tr>
<td>Megace</td>
<td>40-200 mg daily</td>
</tr>
<tr>
<td>Mirena</td>
<td>52 mg over 1-5 years</td>
</tr>
</tbody>
</table>

Meta-Analysis of Progestin Therapy

- 34 observational studies with 408 women with early stage endometrial cancer and 151 CAH\(^1\)
- 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

Regression of Hyperplasia with Mirena

- Cohort study of 344 women treated with Mirena or oral progesterone for CAH or complex hyperplasia\(^1\)
  - 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)
- Meta-analysis of 5 RCTs (377 patients), higher regression rate in non-obese women than oral progesterone (1.41) and similar in obese women (RR 1.03)\(^2\)
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

Metformin in Endometrial Neoplasia

- 19 studies with Metformin
  - Reversion of atypical endometrial hyperplasia to normal endometrium (61.9% to 34.5%)
  - Decreased cell proliferation biomarker staining
  - Metformin using endometrial cancer patients demonstrated higher overall survival (HR=0.82)
- Phase II trial of 17 patients with CAH and 19 with EC
  - MPA (400 mg/day) with metformin (750-2250 mg/day) possibly improves outcomes
  - 81% achieved completed response & 10% relapsed

Comparison of Fertility Sparing Therapies

- Meta-analysis of 54 studies in women with CAH and endometrial cancer
  - 6 studies with hysteroscopic resection (n=6-26)
- Hysteroscopic resection followed by progesterone compared to progesterone alone
  - Higher pooled regression (98.1% vs 77.2%)
  - Increased live birth rate (52.6% vs 33.4%)
  - Lower recurrence rate (4.8% vs 32.2%)
- Pooled live birth rate higher if hysteroscopic resection followed by progesterone than if Mirena only (52.6% vs 18.1%)
  - No difference in regression or recurrence

Surgical Staging in Uterine Cancer

- Total hysterectomy, bilateral salpingo-oophorectomy, sentinel node biopsy +/- pelvic/para-aortic node dissection
- Risk factors to consider
  - Invasion >50% myometrium
  - High grade, serous, clear cell
  - >2 cm tumor size
  - LVSI
  - Cervical involvement
  - Clinically bulky lymph nodes
- Successful sentinel node mapping 86%, sensitivity 97%
Findings at Uterine Cancer Surgery

- Clinical Stage I will be upstaged 30% of the time at time of primary surgery
  - 9% pelvic nodes
  - 6% para-aortic nodes
  - 5% adnexa
  - 12% for positive cytology
  - 6% other (e.g. cervical or abdominal disease)
- Frozen section correlation
  - 97.5% Histology
  - 88% Grade
  - 92.8% Myometrial invasion

Clinical Considerations

- Progestin therapy remains the most tested fertility-sparing option in EIN and early stage endometrial cancer
  - Conservative management should be complemented with referral to an infertility specialist
- Definitive hysterectomy remains the standard of care if appropriate, as up to 40% of patients harbor a co-existing adenocarcinoma and up to 25% fail medical management

A 39 year old P1 female who desires future fertility reports irregular bleeding. Pelvic ultrasound reveals an enlarged uterus. Endometrial biopsy shows complex hyperplasia. You recommend:

A. Provera
B. Mirena IUD placement
C. Hysterectomy
D. Referral to gynecologic oncologist

A 40 year old P0 female who desires future fertility reports irregular bleeding. Endometrial biopsy shows complex hyperplasia. Pelvic ultrasound reveals a thickened endometrial stripe with possible 1.5 cm polypoid mass in the endometrial cavity. You recommend:

A. Provera
B. Mirena IUD placement
C. Hysteroscopy with possible resection
D. Hysterectomy