Treatment of Cervical Intraepithelial Neoplasia

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I have no conflicts of interest

Case
A 26 year old G1P1 woman has an abnormal cytology result. She is referred for a diagnostic workup. Colposcopy is inadequate (unsatisfactory), there is a visible lesion from 12-4 o’clock, and the biopsy shows CIN2. She is on oral contraceptives and has one child. She and her husband want to have another child in the next year.

How would you manage this woman?
A. Repeat colposcopy in 6 months
B. LEEP
C. Ablative therapy
D. Cone biopsy
Goals

- Review literature about obstetrical outcomes of treatments for CIN
- Discuss strategies for management of CIN 2 and CIN 2/3 in reproductive aged women
- Review considerations for determining depth of treatment

Background

- Before the advent of colposcopy, abnormal Paps were treated by hysterectomy or conization
- With the advent of colposcopy, conservative methods were adopted:
  - ablative methods such as cryotherapy, laser ablation, electrocautery or diathermy
  - excision with CO2 laser (laser conization)

Background

- With the introduction of the loop electrosurgical excision procedure (LEEP, LLETZ) in the 1990’s, the ablative methods were mostly abandoned
- Advantages of treatment with LEEP:
  - provides a histological specimen
  - therefore can be used in a “see-and-treat” format

Choice of therapy: excision versus ablation

For ablative therapy (cryotherapy, laser ablation) the following conditions must be present:
- satisfactory colposcopy
- negative endocervical curettage
- lesion fully visualized
- no evidence of invasion
- no glandular dysplasia or glandular atypia
Is ablative therapy effective?

- There is a misperception that cryotherapy is not as effective as LEEP
- Cochrane review 2006 indicated similar rates of residual disease for all treatment modalities

Kyrgiou et al 2006

Treatment outcomes in British Columbia, 6 years of followup

<table>
<thead>
<tr>
<th>Modality used for treatment of CIN 3</th>
<th>Failure rate 21-29 years</th>
<th>Failure rate 30-39 years</th>
<th>Failure rate 40-49 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone biopsy</td>
<td>5.6%</td>
<td>6.3%</td>
<td>8.5%</td>
</tr>
<tr>
<td>LEEP</td>
<td>8.6%</td>
<td>9.6%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Laser</td>
<td>11.7%</td>
<td>13.0%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>24.2%</td>
<td>26.5%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

Melnikow et al JNCI 2009

Choice of treatment modality

- Current literature has suggested that excisional treatment for CIN results in increased risk of preterm delivery

Figure 2 Cumulative forest plot of the relative risk for residual disease for various treatment methods comparisons.23
Obstetric sequelae of cervical therapies: 2006

• Systematic review and meta-analysis of the literature regarding obstetric outcomes after excisional therapy for CIN (cone, loop, laser)
• 27 studies were included
• Preterm birth defined as less than 37 weeks

Kyrgiou et al Lancet 2006

Obstetric sequelae of excisional therapies: meta-analysis 2006

• Results:
  • Cold knife cone was significantly associated with preterm delivery <37 weeks
    – 14% versus 5%, relative risk 2.6 (statistically significant)
  • LEEP was significantly associated with preterm delivery <37 weeks
    – 11% vs 7%, relative risk 1.7 (statistically significant)

Kyrgiou et al Lancet 2006

Obstetric sequelae of excisional therapies: meta-analysis 2006

– Laser ablation: no significantly increased risks for adverse obstetric outcomes were observed

Cochrane review

Kyrgiou et al Lancet 2006
Limitations of the studies:

- Comparison groups were mixed: some studies used “external” controls (population based), which does not control for confounding factors.
- Some studies used “internal” controls (women who were treated before birth versus women who were treated after birth) to avoid some of the confounding.

Obstetric sequelae of cervical treatment: meta-analysis 2011

- Excisional and ablative therapies for CIN
- They separated the results based on the comparison group used in the study: external (population based), internal (birth before versus after treatment), and women with CIN treatment versus no treatment.
- 30 studies- 27 were retrospective.

Obstetric sequelae of excisional therapy for CIN: meta-analysis 2011

- Results:
  - As seen in the other meta-analysis, excisional treatment was associated with a significantly increased risk of preterm labor:
  - RR = approx 2 whether the comparison group was external or internal.
  - The effect of cold knife cone and laser cone (RR 3.41 and 3.58) were more pronounced than LEEP (RR 1.85).

Obstetric sequelae of excisional therapy for CIN: meta-analysis 2011

- Ablative therapy was also associated with a significantly increased risk of preterm labor: RR = 1.47 (statistically significant) when the comparison group was external.
- Ablative therapy was not associated with a significantly increased risk of preterm labor when the comparison group was internal.

Bruinsma and Griffin, BJOG, 2011
Meta-analysis 2008: perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of CIN

- Cold knife cone was associated with significantly increased risk of:
  - Preterm delivery <28 weeks (RR 5.3)
  - Low birth weight <2000 gm (RR 2.9)
  - Perinatal mortality (RR 2.87)

  Arbyn et al, BMJ 2008

Meta-analysis 2008: perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of CIN

- LEEP was associated with non-significantly increased risk of perinatal mortality (1.17, 95% CI 0.74-1.87)
- Cryotherapy and laser ablation were not associated with increased risk of perinatal mortality, preterm delivery, or low birth weight

  Arbyn et al, BMJ 2008

LEEP and risk of preterm birth: U.S. data

- 241,701 singleton births at Parkland Hospital from 1992-2008
  - 511 had previously undergone LEEP
  - 842 subsequently underwent LEEP
- No differences in rates of preterm birth <34 weeks

  Werner et al Obstet Gynecol 2010

Meta-analysis 2014

- 19 studies that were restricted to LEEPs only
- 2 categories of “unexposed” (no LEEP) women were identified-
  - Those with no or unknown history of dysplasia
  - Those with a known history of dysplasia but no excision

  Conner et al Obstet Gynecol 2014
Meta-analysis 2014

- Pooled RR of preterm labor <37 weeks for LEEP was 1.6 (95% CI 1.3-1.9)
- Pooled RR of preterm labor <34 weeks for LEEP was 2.2 (95% CI 1.3–3.7)
- Risk of perinatal mortality was elevated in women with a history of LEEP but not statistically significant (pooled RR 1.6, 95% CI 0.95–2.80).

Conner et al Obstet Gynecol 2014

Meta-analysis 2014

- There were 4 studies in which the “unexposed” group were women with a history of dysplasia but no cervical excision
- No statistically significant difference in the risk of preterm birth when the prior LEEP group was compared to this group (10.0% compared with 7.2%, pooled RR 1.08, 95% CI 0.88–1.33).

Conner et al Obstet Gynecol 2014
Fertility and early pregnancy outcomes
Kyrigou Cochrane reviews 2015

• treatment for CIN did not adversely affect the chances of conception.

• No difference in total miscarriage rate (4.6% versus 2.8%, RR 1.04, 95% CI 0.90 to 1.21; 10 studies, 39,504 participants, low quality)

Obstetrical outcomes after treatment for CIN: Summary of evidence

• There are no randomized trials

• The available studies are limited by retrospective study designs, by the selection of control groups, and by confounding factors

• The biological mechanisms underlying the associations are not yet well understood

Fertility and early pregnancy outcomes
Kyrigou Cochrane reviews 2015

• No difference in first trimester miscarriage rate (9.8% versus 8.4%, RR 1.16, 4 studies, 1103 participants, low quality)

• CIN treatment was associated with an increased risk of second trimester miscarriage (1.6% versus 0.4%, RR 2.60, 95% CI 1.45 to 4.67; 8 studies, 2,182,268 participants, low quality).

Nevertheless the following results have been observed:

Excisional procedures appear to be associated with an increased risk of preterm delivery and perinatal mortality

Excisional procedures appear to be associated with an increased risk of second trimester miscarriage

The data on cryotherapy and laser ablation do not show a strong association with adverse obstetrical outcomes (and in some cases have not been studied)
Goals

- Review literature about obstetrical outcomes of treatments for CIN
- Discuss strategies for management of CIN 2 and CIN 2/3 in reproductive aged women
- Review considerations for determining depth of treatment

CENTRAL TENETS for management of CIN in young women

- The underlying risk of cancer is very low
- HPV infection and CIN lesions are common at the onset of sexual activity
- Clearance of HPV is common
- Approximately 90% of CIN 1 lesions will regress
- Approximately 40% of CIN 2 lesions will regress

ASCP Guidelines for Management of CIN

New ASCCP guidelines 2013:

- In “young women” with high grade CIN, either treatment or observation is acceptable provided colposcopy is satisfactory (adequate)
- When CIN 2 is specified, observation is preferred
- When CIN 3 is specified, or colposcopy is inadequate, treatment is preferred

New ASCCP guidelines 2013:

- “The term ‘young women’ indicates those who after counseling by their clinicians consider risk to future pregnancies from treating cervical abnormalities to outweigh risk for cancer during observation of those abnormalities. No specific age threshold is intended.”
Management guidelines for surveillance of CIN 2 and CIN 2/3 in young women:

- Perform colposcopy and cytology every 6 months.
- If colposcopy worsens or if HSIL persists for one year, repeat colposcopic biopsy, and if it now shows CIN 3, treatment is recommended.
- If CIN 2 persists for 24 months, treatment is recommended.

Figure 17, ASCCP 2013 consensus guidelines

Goals

- Review literature about obstetrical outcomes of treatments for CIN
- Discuss strategies for management of CIN 2 and CIN 2/3 in reproductive aged women
- Review considerations for determining depth of treatment

Effect of size of excision:

- Several studies have shown that the deeper the LEEP or cone, the greater the risk of preterm birth.
- For example, the risk of preterm birth increased 6% for each mm of tissue removed (Noehr et al 2009, Obstet Gyn)
- The height of the cone but not the volume or circumference of the cone was significantly associated with the gestational age at delivery (Ortoft et al BJOG 2010)

"CIN 3 with gland neck extension"

Fig. 1. Diagram illustrating the measurements made on each case:
A. Depth of the deepest crypt.
B. Depth of the deepest involved crypt.

Anderson and Hartley, Obstet Gynecol Survey 1979
Morphometric studies

• Analysis of 319 cone specimens 99.7% of CIN3 lesions were within 4.8 mm of the surface epithelium
• Depth increased with lesion severity: mean depth of CIN1 was 0.4 mm, CIN2 0.9 mm, and CIN3 1.3 mm

Abdul-Karim et al, Obstet Gynecol 1986

Morphometric studies

• Analysis of 342 cone specimens revealed that the mean depth of CIN into the cervical glands was 1.2 mm
• The deepest gland containing CIN that they found was 5.2 mm
• 99.7% of CIN lesions are located 3.8 mm from the surface
• Older women have deeper crypt involvement than younger women

Anderson and Hartley, Obstet Gynecol Survey 1979

Choice of therapy

<table>
<thead>
<tr>
<th>ABLATIVE</th>
<th>EXCISIONAL</th>
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<tbody>
<tr>
<td>Cryotherapy</td>
<td>Loop electrosurgical excision (LEEP)</td>
</tr>
<tr>
<td>CO₂ laser ablation</td>
<td>Cold knife cone biopsy</td>
</tr>
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</table>

Anderson and Hartley, Obstet Gynecol Survey 1979
Cryosurgery (Cryotherapy)

- Historically was the 1st outpatient treatment of CIN
- Low cost, high patient safety
- Easy to perform, well tolerated
- Requires stringent patient selection guidelines
- Clearance rates for CIN = 86% to 91.6%
- Key predictor of success is depth of freeze
Cryotherapy

- Goal is to create sufficient thermal injury to kill abnormal cells
- -20 degrees Celsius necessary for cell death
- For successful ablation, goal is to freeze beyond the lesion

Cryotherapy

- “Iceball” = freeze depth = lateral spread
- Most tissue in this zone will necrose

Cervix

Laser ablation

- CO2 laser is common in dermatology outpatient settings and used to be common in gynecological outpatient practices but has fallen out of fashion since the advent of the LEEP
- Modern equipment is designed for easy use and storage in the outpatient setting
LEEP

- Given the results from the morphometric studies, 99.7% of lesions are ≤5mm deep
- Therefore, in women with satisfactory colposcopy, it would be uncommon to need to excise more than 7 mm of canal
- Routine use of the “top-hat” LEEP should be avoided in women of reproductive age
Case #1

A 26 year old G1P1 woman has an abnormal cytology result. She is referred for a diagnostic workup. Colposcopy is adequate (satisfactory), there is a visible lesion from 12-4 o'clock, and the biopsy shows CIN2. She is on oral contraceptives and has one child. She and her husband want to have another child in the next year.

How would you manage this woman?

A. Repeat colposcopy in 6 months  
B. LEEP  
C. Ablative therapy  
D. Cone biopsy
Case #2

A 26 year old G1P1 woman has an abnormal cytology result. She is referred for a diagnostic workup. Colposcopy is inadequate (unsatisfactory), there is a visible lesion from 12-4 o’clock, and the biopsy shows CIN2. She is on oral contraceptives and has one child. She and her husband want to have another child in the next year.

How would you manage this woman?

A. Repeat colposcopy in 6 months
B. LEEP
C. Ablative therapy
D. Cone biopsy

Case #3

A 26 year old G1P1 woman has an abnormal cytology result. She is referred for a diagnostic workup. Colposcopy is adequate (satisfactory), there is a visible lesion from 12-4 o’clock, and the biopsy shows CIN3. She is on oral contraceptives and has one child. She and her husband want to have another child in the next year.

How would you manage this woman?

A. Repeat colposcopy in 6 months
B. LEEP
C. Ablative therapy
D. Cone biopsy
Questions?