Treatment of Cervical Intraepithelial Neoplasia

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I am on the Scientific and Clinical Advisory Board and have stock options for Oncohealth Inc, a biotech startup developing biomarker tests for cervical cancer screening

Goals

• Discuss treatment options for CIN
• Review literature about obstetrical outcomes of treatments for CIN
• Discuss strategies for individualization of treatment based on patient age, reproductive history, and colposcopy/pathology findings

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, and excision with the 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

Choice of ablative therapy (cryotherapy, laser ablation) requires that the following conditions are met:
  – Satisfactory colposcopy and/or negative endocervical curetage
  – lesion fully visualized
  – no evidence of invasion
  – no evidence of glandular dysplasia or atypia

Is ablative therapy effective?

• There is a misperception that cryotherapy is not as effective as LEEP
• However, the preponderance of the evidence suggests that excisional therapies are associated with adverse obstetrical outcomes
• Cochrane review 2006
**Choice of treatment modality**

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

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**Obstetric sequelae of LEEP: systematic review 2003**

- 5 articles were included in the review
- Findings: women who had LEEP had increased risk of preterm delivery (OR 1.8, 95% CI 1.18-2.76) and low birth weight infants (OR 1.60, 95% CI 1.01-2.52)
- After matching for smoking, preterm birth remained significantly more common (OR 2.53, 95% CI 1.42-4.49)

Crane, Obstet Gynecol 2003;102:1058-62

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**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

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**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 2.59 (95% CI 1.8-3.7)
  - LEEP was significantly associated with preterm delivery <37 weeks
    - 11% vs 7%, relative risk 1.7 (95% CI 1.2-2.3)

Kyrgiou et al Lancet 2006
Obstetric sequelae of excisional therapies: meta-analysis 2006

- Similar but marginally non-significant adverse effects were recorded for laser conisation (relative risk for preterm delivery was 1.71 (95% CI 0.93-3.14).

- laser ablation: no significantly increased risks for adverse obstetric outcomes were observed

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

Bruinsma and Griffin, BJOG, 2011
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 that LEEP (OR 1.85)

Bruinsma and Griffin, BJOG, 2011

• Ablative therapy was also associated with a significantly increased risk of preterm labor: RR = 1.47 (95% CI 1.24-1.74) 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: RR=1.24 (95% CI 0.73-2.10)

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

• 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
Obstetrical outcomes after excisional procedure: internal control group

- Population-based cohort study in Norway
- Spanning the years 1967-2003
- 2,164,000 births
- 15,108 births in women who previously had excision with LEEP, laser or cone biopsy
- 57,136 births in women who subsequently had excision with LEEP, laser or cone biopsy
- The study did not stratify the results by the type of excision performed

Albrechtson et al BMJ 2008

Delivery before 37 weeks:

- 6.2% in the no-excision group
- 17% in the prior-excision group
- 6.7% in the subsequent-excision group

Albrechtson et al BMJ 2008

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)

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
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 association are not yet well understood

Nevertheless the following results have been observed:

– Excisional procedures appear to be associated with an increased risk of preterm delivery and perinatal mortality
– The data on cryotherapy and laser ablation do not show a strong association with adverse obstetrical outcomes
– Depth of excision appears important: deeper is not better in reproductive aged women

For treatment of CIN-

• What is the right depth of treatment to eradicate the disease without imparting unnecessary risk of preterm delivery in reproductive aged women?

Morphometric studies

• Analysis of 319 cone specimens revealed that an excision of 4.80 mm in depth will eradicate 99.7% of CIN3 lesions
• Depth increased with lesion severity: mean depth of CIN1 was 0.42 mm, CIN2 0.93 mm, and CIN3 1.35 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 crypts was 1.24 mm
- The deepest crypt containing CIN that they found was 5.22 mm
- 99.7% of CIN lesions are located 3.80 mm from the surface
- Older women have deeper crypt involvement than younger women

Anderson and Hartley, Obstet Gynecol Survey 1979

Effect of age on treatment outcomes

- In a large retrospective study, failure rates for each treatment modality increased with age
- For ex, for treatment of CIN 3 with LEEP:

<table>
<thead>
<tr>
<th>AGE</th>
<th>FAILURE RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-29</td>
<td>8.6%</td>
</tr>
<tr>
<td>30-39</td>
<td>9.6%</td>
</tr>
<tr>
<td>40-49</td>
<td>12.9%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

Melnikow et al, JNCI 2009

Choice of therapy

<table>
<thead>
<tr>
<th>ABLATIVE</th>
<th>EXCISIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy</td>
<td>Loop excision</td>
</tr>
<tr>
<td>CO₂ laser ablation</td>
<td>(Laser cone biopsy)</td>
</tr>
<tr>
<td>(Electrofulguration, cold coagulation)</td>
<td>Cold knife cone biopsy</td>
</tr>
</tbody>
</table>

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

Effect of age on treatment outcomes

- In a large retrospective study, failure rates for cryotherapy were unacceptably high for women over the age of 40:

<table>
<thead>
<tr>
<th>Modality used for treatment of CIN 3</th>
<th>Failure rate in women aged 40-49 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone biopsy</td>
<td>8.5%</td>
</tr>
<tr>
<td>LEEP</td>
<td>12.9%</td>
</tr>
<tr>
<td>Laser</td>
<td>17.3%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

Melnikow et al JNCI 2009

Laser ablation

- CO2 laser is common in dermatology outpatient settings and used to be common in gynecological outpatient practices but have 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 it would be uncommon to need to excise more than 7 mm of canal
- Routine use of the “top-hat” LEEP should be avoided
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

ASCCP Guidelines for Management of CIN

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.

- 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, treatment is preferred

Observation 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
Case #1

A 31 year old woman has an abnormal cytology result. She is referred for a diagnostic workup. Colposcopy is satisfactory, there is a visible lesion from 12-4 o’clock, and the biopsy shows precancer. 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 treat this woman?
A. Cold knife cone
B. LEEP
C. Laser ablation
D. Cryotherapy

Case #2

• A 48 year old woman has an abnormal cytology result. She is referred for a diagnostic workup. Colposcopy is satisfactory, there is a visible lesion from 12-4 o’clock, and the biopsy shows precancer. She has 3 children and had a tubal ligation after her last delivery.

How would you treat this woman?
A. Cold knife cone
B. LEEP
C. Laser ablation
D. Cryotherapy
Case #3

A 27 year old G0 has an abnormal cytology result. She is referred for a diagnostic workup. Colposcopy is unsatisfactory, there is a visible lesion from 12-4 o’clock, the biopsy shows precancer, and the scraping of the endocervical canal is negative. She is sexually active with her boyfriend and has an intrauterine device for contraception.

How would you treat this woman?

A. Cold knife cone  
B. LEEP  
C. Laser ablation  
D. Cryotherapy

Questions?

Gestational age

Albrechtson et al, BMJ 2008 Norway
Management of CIN 2,3

• CIN 2,3 refers to CIN 2 or CIN 3
• Both excision and ablation are acceptable for women with histological CIN 2,3 and satisfactory colposcopy
• Ablation is unacceptable for women with histological CIN 2,3 and unsatisfactory colposcopy

Recommended management of CIN 2,3 in young women

• Histological diagnosis of CIN 2: observation is preferred but treatment is acceptable
• Histological diagnosis of CIN 2,3: either treatment or observation for up to 24 months with both colposcopy and cytology every 6 months is acceptable, provided the colposcopy is satisfactory
• Histological diagnosis of CIN 3 or colposcopy is unsatisfactory: treatment is recommended

ASCCP Guidelines for Management of CIN 2013
CASE

- 25 year old G0 is referred for a Pap showing HSIL
- Colposcopy

Biopsy showed CIN 2,3

CASE

- 25 year old G0 is referred for a Pap showing HSIL
- Colposcopy;

ECC showed CIN 2,3

CASE

- 25 year old G0 is referred for a Pap showing HSIL
- Colposcopy

Biopsy showed CIN 2,3
Followup after treatment

- Review melnikow
- Review ASCCP guidelines

Factors not associated with preterm delivery

- Time since LEEP was NOT associated with preterm delivery (Noehr et al Obstet Gynecol 2009)
- The circumference and volume of the cone were NOT associated with preterm delivery (Ortoft et al BJOG 2010)

Obstetrical outcomes after excisional procedure- Denmark

- Population based cohort study at Aarhus University Hospital (8% of all Danish births)
- 721 deliveries after 1 cone, 37 deliveries after 2 cones, 74,552 deliveries after no dysplasia or treatment
- 572 had LEEPs, 71 electrosurgical needle procedures, 67 cold knife cone
- Outcomes: GA, birth weight, perinatal mortality

Obstetrical outcomes after excisional procedure- Denmark

<table>
<thead>
<tr>
<th></th>
<th>RR for Preterm delivery &lt;37 weeks</th>
<th>RR for Preterm delivery &lt;28 weeks</th>
<th>RR for Perinatal mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>One cone</td>
<td>2.8</td>
<td>4.9</td>
<td>2.8 overall 9.9 for GA&lt;28 weeks</td>
</tr>
<tr>
<td>Two cones</td>
<td>9.9</td>
<td>9.8</td>
<td></td>
</tr>
</tbody>
</table>

Ortoft et al, 2010 BJOG
Cryotherapy

- CIN may penetrate glands 3.6-3.8mm
- Cell death to 4mm eradicates 99.7% of lesions
- Goal: 5mm iceball with a double freeze

CO₂ Laser Ablation

- Treatment of choice for CIN in 1980s
- Excellent for large cervical lesions, vaginal lesions, and difficult to access lesions
- Clearance rates high
  - Success rates of 90% to 96%, similar to other modalities

Cryotherapy

- After treatment, copious watery vaginal discharge for up to one month is common
- Bleeding and infection are rare

- Success more related to
  - lesion size than to lesion grade
  - absence of lesion 4 to 5 mm into canal
- Other than large lesion size and extension into the canal, treatment failure is most commonly secondary to inadequate freeze
From Castenon BMJ 2012

- After adjusting for confounding, the increased risk of preterm delivery in births after treatment for cervical intraepithelial neoplasia ceases to exist.
- There is only a small chance (2.5%) that the risk of preterm delivery is increased by more than 3.5 per 100 births in women treated in England.
- The relative risk here is significantly less than reported previously possibly because colposcopy treatment is quality assured.