Treatment of Cervical Intraepithelial Neoplasia

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for
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I have no conflicts of interest

Goals

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

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, ablative methods 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?

- Cochrane review 2006

Figure 2 Cumulative forest plot of the relative risk for residual disease for various treatment methods comparisons.23

Kyrgiou et al 2006
Choice of treatment modality

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

Obstetric sequelae of LEEP: systematic review 2003

• 5 articles included in the review
• Findings: women who had LEEP had increased risk of preterm delivery (OR 1.8, 95% CI 1.2-2.8) and low birth weight infants (OR 1.6, 95% CI 1.0-2.5)
• After matching for smoking, preterm birth remained significantly more common (OR 2.5, 95% CI 1.4-4.5)

Crane, Obstet Gynecol 2003;102:1058-62

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 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 significantly associated with preterm delivery <37 weeks
  – 14% versus 5%, relative risk 2.6 (95% CI 1.8-3.7)
• LEEP significantly associated with preterm delivery <37 weeks
  – 11% versus 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 adverse effects 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 observed

Kyrgiou et al Lancet 2006

Limitations of the studies

- Comparison groups mixed: some studies used “external” controls (population based), which may not control well 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
- Separated 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 associated with a significantly increased risk of preterm labor:
  - RR = approx 2 whether the comparison group was external or internal
  - Effect of cold knife cone and laser cone (RR 3.41 and 3.58) more pronounced than LEEP (RR 1.85)

Bruinsma and Griffin, BJOG, 2011

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**Control group is important**

- Ablative therapy 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 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

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

Cold knife cone 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

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

- LEEP associated with no increased risk of perinatal mortality (1.17, 95% CI 0.74-1.87)
- Cryotherapy and laser ablation not associated with increased risk of perinatal mortality, preterm delivery, or low birth weight

Arbyn et al, BMJ 2008
Effect of size of excision

• 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 Gynecol)
• Height of the cone but not the volume or circumference of the cone 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

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

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 elevated in women with a history of LEEP but not statistically significant (pooled RR 1.6, 95% CI 0.95–2.80).
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 (pooled RR 1.08, 95% CI 0.88–1.33).

LEEP-to-pregnancy interval and obstetrical risks

• Multicenter retrospective cohort study 1996-2006
• 596 women had previously undergone LEEP and subsequently became pregnant
• Median time to pregnancy was 30.8 months (interquartile range 18.4-50.7)
• LEEP-to-pregnancy interval (<12 months versus ≥ 12 months) not associated with risk of preterm labor

LEEP-to-pregnancy interval and risk of spontaneous abortion

• LEEP-to-pregnancy interval of less that 12 months significantly associated with an increased risk of SAB (<12 weeks): 17.9% versus 4.6%, OR 5.6 (2.5-12.7)
• LEEP-to-pregnancy interval of less that 6 months showed an even stronger effect: 42.9% versus 4.3%, OR 16.8 (3.5-81.6) but the number of pregnancies in the 6 mo group was small (n=7)

Obstetrical outcomes after treatment for CIN: Summary of evidence

• No randomized trials
• Studies limited by retrospective designs, by the selection of control groups, and by confounding factors
• Biological mechanisms underlying the association not 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
- Shorter interval to subsequent pregnancy after LEEP (<12 months) may increase the risk of first trimester spontaneous abortion
- Data on cryotherapy and laser ablation do not show a strong association with adverse obstetrical outcomes

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 glands was 1.24 mm
- The deepest gland 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 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

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: create sufficient thermal injury to destroy abnormal cells
• -20 degrees Celsius necessary for cell death
• For successful ablation: freeze beyond the lesion

Cryotherapy

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

Courtesy E.J. Mayeux
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 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 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 in women with satisfactory colposcopy
- Routine use of the “top-hat” LEEP should be avoided in women of reproductive age

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

- 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

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

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.”

Case #1

A 31 year old 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.
Case #2

A 26 G1P1 year old 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 treat this woman?

1. Observation
2. LEEP
3. Laser ablation
4. Cryotherapy
5. Cone biopsy

Questions?
Case #3

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 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 treat this woman?

Case #4

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 CIN 2/3. She has 3 children and had a tubal ligation after her last delivery.

How would you treat this woman?
In conclusion, results of this systematic review and meta-analysis of the current body of literature suggest that the notion that LEEP increases the risk of preterm birth needs to be reevaluated. Our results indicate that the increased risk for preterm birth before 37 weeks of gestation in women with a history of LEEP may be related to shared risk factors rather than the cervical excision procedure itself. Larger studies with carefully selected comparison groups that are similar to women with a history of LEEP would further clarify the relationship between LEEP and preterm birth. Additionally, patient-level data could

Conner et al Obstet Gynecol 2014