Treatment of Dysplasia

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Disclosures

• I am on the Clinical and scientific advisory Board of OncoHealth Inc, a biotech startup that is developing a diagnostic test for cervical cancer screening.

Goals

• Discuss treatment options for cervical dysplasia
• Review literature about obstetrical outcomes of treatments for CIN
• Discuss treatment guidelines for adolescents and young women

CASE

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

Biopsy showed CIN 2,3
**What would you do next?**

- HPV test
- Follow-up in 6 months with cytology and colposcopy
- Treat
  - LEEP
  - Cone biopsy
  - Cryotherapy
  - Laser ablation
  - Laser cone

**Choice of therapy**

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**Advantages of excisional therapy**

- Allows histological assessment exact grade of disease present—hence compensates for inaccuracies in colposcopic impression
- Allows “see and treat” approach
- Allows assessment of margins
- Allows the diagnosis of occult cancer

**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 ECC
- Lesion fully visualized
- No evidence of invasion
Choice of therapy: excision versus ablation

- Isn’t the effectiveness of LEEP or cold knife cone better than cryotherapy?

Efficacy: Loop vs Cryotherapy vs Laser

- Randomized clinical trial of loop versus laser vaporization versus cryotherapy
- 120-140 patients in each arm
- Randomization stratified by lesion size, endocervical gland involvement, and SIL grade
- No difference in complications, recurrence or persistence

Mitchell et al, 1998 Obstet Gynecol 92; 737-44
Why choose ablative therapy?

• The preponderance of the evidence suggests that excisional therapies are associated with adverse obstetrical outcomes

Obstetric sequelae of excisional therapy for CIN

• Retrospective cohort study (Australia)
• Risk of pPROM was significantly increased following treatment with laser conization (aRR, 2.7) or LEEP (aRR 1.9), but not laser ablation (aRR, 1.1).
• Not associated with preterm delivery

Sadler et al 2004 JAMA

Obstetric sequelae of LEEP

• Retrospective cohort study from Halifax Canada
• LEEP associated with preterm deliver (7.9% versus 2.5%)
• LEEP associated with preterm delivery after premature rupture of membranes (3.5% versus 0.9%)

Samson et al 2005 Obstet Gynecol

Obstetric sequelae of excisional therapy for CIN: meta-analysis

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

Kyrgiou et al Lancet 2006
Obstetric sequelae of excisional therapy for CIN: meta-analysis

- LEEP was significantly associated with:
  - preterm delivery: 11% vs 7%,
  - low birthweight (<2500 g) 8% vs 4%
  - premature rupture of the membranes 5% versus 2%

Kyrgiou et al. Lancet 2006

Obstetric sequelae of excisional therapy for CIN: meta-analysis

- Cold knife cone was significantly associated with
  - preterm delivery 14% versus 5%, RR 2.59
  - low birth-weight RR 2.53
  - caesarean section RR 3.17

Kyrgiou et al. Lancet 2006

Obstetric sequelae of excisional therapy for CIN: meta-analysis

- Similar but marginally non-significant adverse effects were recorded for laser conisation (preterm delivery 1.71, 0.93-3.14).
- No significantly increased risks for obstetric outcomes after laser ablation.

Kyrgiou et al. Lancet 2006

Cochrane review

The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia

A
Preterm delivery (<37 weeks)
Cesarean delivery
PPROM
Preterm labour
Perinatal mortality
NICU admission

LEEP Laser conisation Laser ablation Knife conisation
**Preterm delivery after surgical treatment for CIN**

- Prospective cohort study (Norway) of 11,088 women beginning in 1991
- 14,982 births
- Follow-up through 2004

Nohr et al 2007 Acta Obstet Gynecol Scanda

**Preterm delivery after surgical treatment for CIN**

- Prior preterm birth was strongest risk factor (OR=2.3, 95% CI 1.4-3.7)
- Incidence of preterm birth was 3.5% in women with no prior LEEP versus 6.6% in women following LEEP (OR 1.8, 95% CI 1.1-2.9)


**Preterm delivery after surgical treatment for CIN**

- Retrospective registry study from Finland
- 25,827 women with surgical therapy for CIN from 1986-2003
- 8210 singleton births
- Risk of preterm labor increased after cold knife/LEEP cone (RR 2.1 fold for <28 weeks)
- Risk of perinatal mortality increased after cone (RR 1.74)

Jakobsson et al, Obstet Gynecol 2007

**Obstetrical outcomes after excisional procedure**

- Population-based cohort study in Norway
- Spanning the years 1967-2003
- 2,164,000 births
- 15,108 births in women who previously had cone biopsies
- 57,136 births in women who subsequently had cone biopsies

Albrechtson et al BMJ 2008
Gestational age

Delivery before 37 weeks:
- 6.2% no cone
- 17% prior cone
- 6.7% subsequent cone

Albrechtson et al, BMJ 2008

Birth weight

Albrechtson et al, BMJ 2008

Relative risk of preterm birth after cone versus no cone- Norway

Albrechtson et al, BMJ 2008

Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis

- Cold knife cone associated with 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
Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis

- LEEP was not significantly associated with increased risk of perinatal mortality, preterm delivery, or low birth weight
- Ablative therapies were not significantly associated with increased risk of perinatal mortality, preterm delivery, or low birth weight

Arbynt et al, BMJ 2008

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 cones
- 572 had LEEPs, 71 electrosurgical needles procedure, 67 cold knife cone
- Outcomes: GA, birth weight, perinatal mortality

Ortoft et al, 2010 BJOG

<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>
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<tr>
<td>One cone</td>
<td>2.8</td>
<td>4.9</td>
<td>2.8 overall</td>
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<tr>
<td>Two cones</td>
<td>9.9</td>
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Ortoft et al, 2010 BJOG

Obstetrical outcomes after excisional procedure- Denmark

- The time interval between the conisation and the first pregnancy after conisation varied between 99 and 4891 days (13 years), with a median of 1059 days (2.9 years). No association was found between the number of days from the conisation to delivery and the gestational age at birth.

Ortoft et al, 2010 BJOG
Obstetrical outcomes after excisional procedure - Denmark

- The height of the cone was associated with significantly associated with the gestational age at delivery
- Circumference and volume of the cone were NOT associated with gestational age at delivery

Ortoft et al, 2010 BJOG

Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous preterm delivery: Denmark

- Registry based study of all deliveries form Denmark from 1999-2005: 552,678 singleton deliveries
- Increasing cone depth was associated with a significant increase in the risk of preterm delivery
  - Adjusted odds ratio of 1.06 (1.03-1.09) of preterm birth for each mm of tissue removed

Noehr et al Obstet Gynecol 2009

Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous preterm delivery: Denmark

- Time since LEEP was not associated with preterm delivery
- Two or more LEEPs increased the risk almost fourfold for subsequent preterm delivery (versus no LEEP)

Noehr et al Obstet Gynecol 2009

Loop electrosurgical excision procedure and risk of preterm birth

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

Werner et al Obstet Gynecol 2010
Obstetrical outcomes after treatment for CIN: Summary of evidence

- There are no randomized trials
- Excisional procedures appear to be associated with an increased risk of preterm delivery and perinatal mortality
- The data on ablative procedures are more limited but do not show a strong association with adverse obstetrical outcomes
- Depth of excision may be important: deeper is not necessarily better in reproductive aged women

Choice of therapy

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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

(Courtesy E.J. Mayeux)
Cryotherapy

- 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

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

Cryoprobe

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

Cryotherapy

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

**Outpatient laser ablation**

- Intracervical Block (same as for LEEP):
  - Inject the cervix at the anticipated surgical margin with 1% lidocaine

X=Injection site
Recommended 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
• Hysterectomy is unacceptable as primary therapy for CIN 2,3

ASCCP Guidelines for Management of CIN, AJOG 2007

Recommended management of CIN 2,3

• Observation of CIN 2,3 with sequential cytology and colposcopy is unacceptable
• EXCEPT
• During pregnancy
• In adolescents and young women

ASCCP Guidelines for Management of CIN, AJOG 2007

CENTRAL TENETS for management of CIN in adolescents and 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, AJOG 2007
Recommended management of CIN 2,3 in adolescents and 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, AJOG 2007

Recommended management of CIN 2,3 in pregnancy

- In the absence of invasion, colposcopy and cytology every 12 weeks is acceptable
- Deferring reevaluation until at least 6 weeks postpartum is acceptable
- Repeat biopsy is recommended only if the lesion appears worse or the cytology suggests invasion
- Diagnostic excisional procedure is recommended ONLY if invasion is suspected

ASCCP Guidelines for Management of CIN, AJOG 2007

CASE

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CASE

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

ECC showed CIN 2,3

What would you do next?

- Follow-up in 6 months with cytology and colposcopy?

OR

- Treat?
  - LEEP
  - Cone biopsy
  - Cryotherapy
  - Laser ablation

What would you do next?

- Follow-up in 6 months with cytology and colposcopy?

- Treat?
  - LEEP
  - Cone biopsy
  - Cryotherapy
  - Laser ablation
CASE

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

Biopsy showed CIN 2,3
Excisional therapy: Loop versus cone

- Relative contraindications to loop excision are patients in which invasion is suspected or the patient has a glandular abnormality on Pap (atypical glandular cells, adenocarcinoma in situ). The general consensus is that these patients should have a cold knife cone biopsy in order to get optimal information about the margins and depth of invasion.

Cone Biopsy by Loop Excision

- Single pass for transformation zone
- Then deeper pass for endocervical canal
- Can be safely performed in the office

Considerations for adolescents

- Now screening before the age of 21 (ACOG)
- No HPV testing in women <21 years for ASCUS triage
- Management of CIN 1 is conservative
Efficacy: Loop Excision versus Cryotherapy

- Cost is significantly lower for cryotherapy due to pathology charges incurred by analysis of loop tissue
- Loop has the benefit of possibility of diagnosing microinvasive disease
- Loop is not associated with prolonged vaginal discharge common after cryotherapy

Efficacy: Loop excision versus cone biopsy

- Randomized prospective study was published in 1999 comparing cold-knife cone (CKC) to loop excision
- N=85 for CKC and 89 for loop
- No differences in subsequent development of disease (CIN, invasive cancer, ACIS)
- No difference in subsequent rates of satisfactory colposcopy (46% vs 37% for CKC vs loop)
- Complication rates were comparable
  - Major surgical complication: 1 in each group
  - Rate of delayed bleeding was 9 versus 10% (NS)
  - Infection rate was 1% in each group

Mitchell et al, 1998 Obstet Gynecol 92; 737-44