

# Treatment of Dysplasia

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## Goals

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

## Choice of therapy

ABLATIVE	EXCISIONAL
Cryotherapy	Loop excision
CO <sub>2</sub> laser ablation	Laser cone biopsy
(Electrofulguration, cold coagulation)	Cold knife cone biopsy

## 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

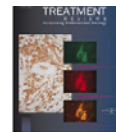
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ANTI-TUMOUR TREATMENT

### The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: The cochrane colposcopy & cervical cytopathology collaborative group (C5 group) approach

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## **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

## **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 Scand

## **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)

**Nohr et al Acta Obstet Gynecol Scand 2007**

## **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

## **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

Arbyn 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

## Obstetrical outcomes after excisional procedure- Denmark

	RR for Preterm delivery <37 weeks	RR for Preterm delivery <28 weeks	RR for Perinatal mortality
One cone	2.8	4.9	2.8 overall 9.9 for GA<28 weeks
Two cones	9.9	9.8	

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.**

- Registry based study of all deliveries from Denmark from 1999-2005: 552,678 singleton deliveries
- increasing cone depth was associated with a significant increase in the risk of preterm delivery

Noehr et al Obstet Gynecol 2009

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

- 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

ABLATIVE	EXCISIONAL
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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

## **Cryotherapy**

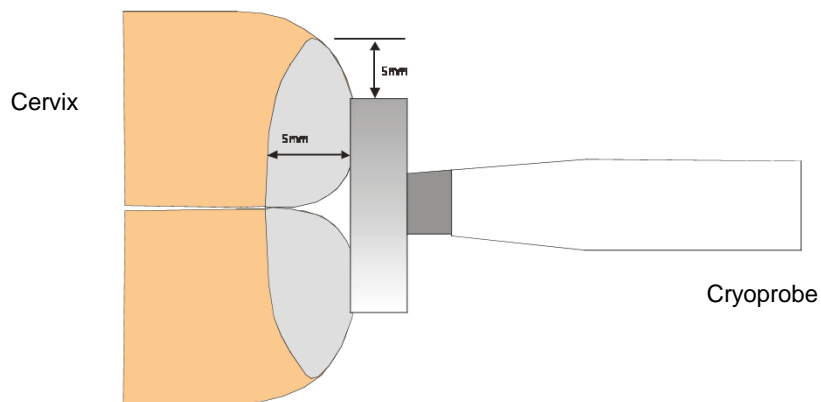
- Success more related to
  - lesion size than to lesion grade
  - absence of lesion 4 to 5 mm into canal
- Other than large lesion size and extension into the canal, treatment failure is most commonly secondary to inadequate freeze

## 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



Courtesy E.J. Mayeux

## **Cryotherapy**

- CIN may penetrate glands 3.6-3.8mm  
Boonstra H. Obstet Gynecol 1990; 75:227-31; Anderson MC. Obstet Gynecol 1990; 55:546-50.
- 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

## **CO<sub>2</sub> 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

## **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 adolescents and young women**

- For observation of CIN 2 or CIN 2,3 lesions, if the colposcopic lesion worsens, or HSIL cytology or high grade lesion persists for 1 year, repeat biopsy is indicated
- Treatment is recommended if CIN 3 is subsequently diagnosed, or if CIN 2,3 persists for 24 months
- After 2 consecutive normal/negative cytology results and normal colposcopy, return to routine screening

**ASCCP Guidelines for Management of CIN, AJOG 2007**

# CASES