Management of young women with CIN2

Peter Sykes
NCSP Colposcopy Symposium 2012
A prospective trial of conservative management in young women with CIN2.

- Predicting Regression
- In CIN E 2 S

Inclusion Criteria
- Age under 25 at first visit.
- No prior high grade histological or cytological abnormality prior to this referral.
- Biopsy proven CIN 2.
- Entire lesion accessible to colposcopy.
- Participants in study agree to six monthly colposcopy and cervical smear and biopsy for a total of two years.
- Cytology and pathology reviewed at multidisciplinary meeting. (no suspicion of glandular abnormality biopsy consistent with cytology)
- Signed informed consent.
Aims /outcome measures

Study Aims
• To document the safety of follow-up of CIN 2 in young women under the age of 25. (550)
• To identify the rate of regression of CIN 2 in this group of women.
• To identify predictors of regression and progression of CIN 2 in this cohort.

Primary outcome measures
• Proportion whose lesions regress to CIN1 and normal within 24 months of follow up.
• Proportion who are lost to follow up (greater than 9 months) during the study.

Secondary outcome measures
• Proportion of study participants who require treatment during 24 month period
• The reason treatment is required.
• The proportion of the eligible women included in the study and reasons for exclusion
• Correlation of clinical factors with regression
• Correlation of cytology/pathology factors with regression,
• Correlation of above factors and requirement for treatment (for CIN3 or worse).
INITIAL VISIT - Pre-study
Potential Participants

Under 25
Referral to colposcopy for abnormal cytology
↓
cytology, colposcopy, biopsy
↓
Possible CIN2 = study information given to woman

Biopsy = CIN 2

? Eligible patient
Check inclusion/exclusion criteria
Results discussed
Offer study entry

Criteria not met
- not eligible

Study Participant
Consent form signed
CRF ELIGIBILITY FORM & BASELINE DATA FORM
To be completed

MDM review within 4 weeks
Review of cytology & histology
Send cytology vial to Christchurch

CIN1 or less
CIN3 or worse suspected
Exclude & complete CRF COMPLETION FORM
safety

• Informed consent
• Exclusion criteria
• Multidisciplinary review
• More than one biopsy
• 2 addresses
• Careful follow up
• SAE forms
• Study monitoring
• Stopping rules
• Long term FU as per NCSP guidelines (previous HG)
Multicenter study

- Peter Sykes, Bryony Simcock
- Dianne Harker
- Helene McNabb Christchurch
- Simone Petrich Dunedin
- Viki Robertson, Grey Hosp
- Narena Dudley, Hamilton
- Jim Faherty Invercargil
- Dean Maharaj / Dianne Kenwright Wellington
- Lynn Sadler


- Cancer society grant
Important study.
we would like to enrol our patients.
The treatment of CIN2 in a 22 year old woman is criminal.
CIN2 should be considered Low grade.

Ill conceived
A risk to patients
CIN2 does not exist
CIN2/3 should be considered one entity
Diagnosis non reproducible
Too much work
Stressful for women
How did we get here

• Known regression CIN2
• Recognition of harm from treatment
• CIN2 Frequent diagnosis in young nulliparous women
• Low incidence Cancer in young women
• Limited efficacy of screening in young women
• Conservative management in adolescent women
• Increasing practice of conservative management
NCSP independent monitoring report  
July-Dec 2009

<table>
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<tr>
<th>Histology Category</th>
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<th>20-24</th>
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<td>1,173</td>
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<td>10,652</td>
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Adverse pregnancy outcomes associated with treatment CIN

3. Adjusted odds ratios (95% CI) for the association between cervical procedures and extremely, very, and moderate spontaneous preterm delivery

<table>
<thead>
<tr>
<th>Variable</th>
<th>All deliveries (n)</th>
<th>Extremely preterm(^b) (n = 1373)</th>
<th>Very preterm(^c) (n = 1665)</th>
<th>Moderately preterm(^d) (n = 16,011)</th>
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<tr>
<td></td>
<td></td>
<td>n (95%)</td>
<td>n (95%)</td>
<td>n (95%)</td>
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<td><strong>LEEP vs no LEEP</strong></td>
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<td>No LEEP</td>
<td>544,498</td>
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<td>3.16 (2.27-4.40)</td>
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<tr>
<td><strong>Selected procedures vs no procedures</strong></td>
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<td>50</td>
<td>3.23 (2.32-4.50)</td>
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</table>

Noehr. LEEP and spontaneous preterm delivery. Am J Obstet Gynecol 2009.\(^a\) N = 552,678;

\(^e\) adjusted for calendar time, maternal age at delivery, smoking during pregnancy, and marital status during pregnancy.
Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis

*BMJ;337:a1284*
Very low risk of cancer under the age of 25

Figure 5.4: Incidence of cervical cancer (age-specific), by age, women 20–85+ years, 1992–1996 and 2002–2006
Screening in women under 25 not associated with decreased incidence of cervical cancer.

P Sasieni BMJ 2009;339:b2968
## Regression of CIN2

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Regression rate</th>
<th>Age range</th>
<th>Time period</th>
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<td>Moscicki AB</td>
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<td>13-24</td>
<td>2 yrs</td>
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<td>Guedes AC</td>
<td>2007</td>
<td>42%</td>
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<td>Monteiro</td>
<td>2010</td>
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<td>11-19</td>
<td>2yr</td>
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<td>Moore k</td>
<td>2007</td>
<td>65%</td>
<td>13-21</td>
<td>1.5 yr</td>
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<td>Discacciati M</td>
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<td>17-47</td>
<td>1 yr</td>
<td>42</td>
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<td>Fuchs K</td>
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<td>11-20</td>
<td>2yr</td>
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<tr>
<td>Castle P*</td>
<td>2009</td>
<td>40%</td>
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<td>2yr</td>
<td>357*</td>
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</table>
NZ retrospective study

Objective:
• To review the outcome of (CIN) 2 in women under 25 managed conservatively.

Study Design:
• Analysis comparing women who had immediate treatment with those whose treatment was deferred more than 4 months.
• The primary outcome measure was spontaneous regression of CIN2.
• Secondary outcomes were treatment rates and loss to follow-up.

findings

• 452 women under 25 with CIN2
• Median age 21
• 256 (57%) received immediate treatment,
• 157 (35%) conservative management
• Median follow up 8 months
• 39 (9%) management was unknown.
• Younger nulliparous women more likely to be managed conservatively
Immediate treatment 256
histology 232

- Median time to treatment was 2 months.
- Treatment histology CIN2 44%,
- Normal 2.5%, CIN1 /HPV 20%
- CIN3 (28%).
- 2 cases were AIS
- 1 case of 1a1 microinvasive squamous cancer.
Conservative management greater than 4 months

Final histology/cytology

- Normal 35%
- CIN1/HPV 27%
- CIN2 20%
- CIN3 18%

Median time to treatment 7 months (41%)

- Lost to follow up 3%

Smoking status and referral smear not associated with regression
There is a need for large multicenter prospective studies prior to the incorporation of conservative management into common practice.

• In a prospective manner what proportion of CIN2 lesions will regress under conservative management?
• What proportion of women will undergo conservative management?
• In a multicenter study what proportion of women will be lost to follow up?
• Is there an identifiable risk to women?
• Can we identify a group of women more likely to regress?
• Does conservative management negatively impact on quality of life?
• What are the cost implications of conservative management?
Currently HPV status most predictive

- 20/42 patients with HPV 16/18 showed early clearance
- Of these, 90% had clearance of their CIN 2
- But at least 50% of those with persistent HPV 16/18 had regression
What is CIN2?

Agreement of CC and QC Pathology Biopsy Diagnoses for the Worst Cervical Biopsy Results for Each Woman Participating in ALTS*

<table>
<thead>
<tr>
<th>CC Pathology Biopsy Diagnosis</th>
<th>Normal (n = 1,105)</th>
<th>ASC (n = 27)</th>
<th>CIN 1/LSIL (n = 628)</th>
<th>CIN 2 (n = 227)</th>
<th>CIN 3+ (n = 203)</th>
<th>Total (n = 1,134)</th>
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<td>1,105 (32)</td>
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<td>10 (0)</td>
<td>9 (0)</td>
<td>4 (0)</td>
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<tr>
<td>Carc HPV+ (%)</td>
<td>37</td>
<td>50</td>
<td>56</td>
<td>75</td>
<td>50</td>
<td>312</td>
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<tr>
<td>HPV-16+ (%)</td>
<td>7</td>
<td>0</td>
<td>11</td>
<td>13</td>
<td>25</td>
<td>33</td>
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<tr>
<td>ASC (%)</td>
<td>249 (7)</td>
<td>27 (1)</td>
<td>28 (1)</td>
<td>5 (0)</td>
<td>3 (0)</td>
<td>312</td>
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<tr>
<td>Carc HPV+ (%)</td>
<td>49</td>
<td>54</td>
<td>59</td>
<td>80</td>
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<td>312</td>
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<tr>
<td>HPV-16+ (%)</td>
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<td>0</td>
<td>15</td>
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<td>0</td>
<td>12</td>
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<tr>
<td>CIN 1/LSIL (%)</td>
<td>463 (13)</td>
<td>15 (0)</td>
<td>628 (18)</td>
<td>83 (2)</td>
<td>13 (1)</td>
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<td>76</td>
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<td>HPV-16+ (%)</td>
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<td>16</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CIN 2 (%)</td>
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<td>14 (0)</td>
<td>105 (3)</td>
<td>227 (7)</td>
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<td>57</td>
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<td>95</td>
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<td>HPV-16+ (%)</td>
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<td>32</td>
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<td>CIN 3+ (%)</td>
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<td>6 (0)</td>
<td>59 (2)</td>
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<td>100</td>
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<td>777</td>
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P Castle

Biopsy correlates poorly with loop specimen

<table>
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<th>QC review of biopsy specimen</th>
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<th>CIN 3</th>
<th>Total</th>
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<td>61 (46.2)</td>
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<td>CIN 3</td>
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<td>Total</td>
<td>240</td>
<td>120</td>
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<td>492</td>
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A pragmatic and simplistic view!

CIN1
• An acute viral infection
• Likely to regress
• Conservative management recommended

CIN2

CIN 3
• Associated with persistent HPV infection.
• Unlikely to regress
• Associated with significant risk of invasion
• Treatment recommended
My opinion

- Many young women with CIN2/ HSIL will undergo spontaneous regression.
- Political risk to non-screening in under 25s (7 cases 2010/11).
- Vaccination rates currently too low to have major impact.
- Currently conservative management of CIN2 cannot be considered standard treatment.
- Those wishing to offer conservative management should enrol patients in Princess.