Preserving the Gateway to Life: HPV Prevention and Escharotic Treatment of Cervical Dysplasia

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AANP Conference 2013
Keystone, CO
As a Naturopathic Midwife I get to hang out with a lot of cervixes...
Most times they behave beautifully
Sometimes they don’t

We may end up in hospital for induction, pain medication, or in some cases, cesarean delivery.
So, what makes the difference?
My Personal Practice
Thought Triggering Birth Experience

- Second labor (same mom) I almost missed the labor, “I could do that a hundred times”.
- Had these births happened in hospital, the first would more than likely have been a cesarean delivery and the second, very likely a repeat cesarean delivery.
My Personal Practice
Thought Triggering Pap Experiences

• Paps on women with os so small the cyto brush won’t go in, even with a good deal of pressure
• Escharotic treatment on one of these women: normal cycles, no cramping until after cone biopsy healed, ever after severe cramping...AND her pap only remained normal after the procedure for a short time.
• After E tx., much improved menstrual symptoms, normal pap result
Cervical Stenosis Definitions

• Stenosis was considered present if manual dilation was required to allow endocervical sampling with an endocervical curette 3 mm wide¹

• Stenosis was defined as cervical narrowing which could not admit a 2.5 mm-diameter Hegar's dilator ²

1. Risk Factors for Cervical Stenosis After Loop Electrocautery Excision Procedure
Suh-Burgmann, Elizabeth J. MD; Whall-Strojwas, Denise RN; Chang, Yuchiao PhD; Hundley, Drew MD; Goodman, Annekathryn MD

2. Risk of Cervical Stenosis After Large Loop Excision or Laser Conization
Baladuf, Jean-Jacques; Dreyfus Michel; Ritter Jean; Meyer, Pierre; Philippe, Emile
Cervical Os

- Non-parous
- Parous
- Stenotic

That’s probably not the cervix, try higher or lower.
“Cervical Stenosis or atresia can be a true cause of cervical dystocia. This is not a rare complication of pregnancy, and although it is a significant factor leading to prolonged labor, cervical lacerations or rupture of the lower uterine segment, it has received little attention to the English literature.”

Cervical procedures: Cold Knife vs. Laser vs. LEEP

These results suggest that:

- laser conization is relatively costly and time consuming and alters the tissues significantly

- the choice between cold knife and LEEP is more difficult—cold knife gives a sample adequate for histological evaluation (including evaluation of the margins)

- while the LEEP procedure is technically easier and less time consuming but sometimes induces electrocautery artifact so that evaluation of the margins is not possible.

A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP.
Two hundred fifty-five women treated by laser conization and 277 treated by loop electrosurgical excision procedure were followed regularly by postoperative colposcopy for mean periods of 38 and 16 months, respectively. Stenosis was defined as cervical narrowing that prevented insertion of a 2.5-mm Hegar dilator.

Thirty-eight cases of cervical stenosis, of which seven were complete, were diagnosed up to 28 months after treatment.

The risk of postoperative cervical stenosis was higher for patients over 50 years of age (P = .031), for those with a totally endocervical lesion (P = .001), for those with an excision 20 mm high or greater (P = .005), and for those with laser conization (P = .009).

Parity, menopause, previous treatment for cervical intraepithelial neoplasia, satisfactory colposcopy, size of the lesion, its histologic diagnosis, and the extent of excision did not increase the risk for cervical stenosis.

Excision was not as high with loop electrosurgical excision as with laser conization (14.3 +/- 5.0 mm versus 20.2 +/- 6.0 mm). The height of excision (P = .04) and a totally endocervical lesion (P = .001) were the only independent factors associated with postoperative stenosis identified by a multivariate analysis using logistic regression.

Conclusion: The height of excision and a totally endocervical lesion were the main factors associated with cervical stenosis. The decreased risk associated with the loop electrosurgical excision procedure seems to be due to a shorter endocervical excision.
Risk Factors for Cervical Stenosis After LEEP Colposcopy Clinic at MA General Hospital (2000)

• Stenosis was considered present if manual dilation was required to allow endocervical sampling with an endocervical curette 3 mm wide

• The average age was 32 years. Cervical stenosis occurred in ten of 164 women (6%)

• Among factors analyzed, previous loop excision and volume of excision specimen were the only independent predictors of stenosis.
### Table 1. Incidence of Stenosis After Loop Electrocautery Excision

<table>
<thead>
<tr>
<th>Characteristic (n = 164)</th>
<th>Women with stenosis n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 76)</td>
<td>3 (4)</td>
<td>.34</td>
</tr>
<tr>
<td>No (n = 88)</td>
<td>7 (8)</td>
<td></td>
</tr>
<tr>
<td>OC user</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 43)</td>
<td>2 (4.6)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>No (n = 121)</td>
<td>8 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 59)</td>
<td>2 (3.4)</td>
<td>.33</td>
</tr>
<tr>
<td>No (n = 105)</td>
<td>8 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe dysplasia (n = 80)</td>
<td>8 (10)</td>
<td>.053</td>
</tr>
<tr>
<td>Other (n = 84)</td>
<td>2 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

OC = oral contraceptive.

### Table 2. Comparison of Loop Excision Dimensions and History

<table>
<thead>
<tr>
<th>Excision dimension</th>
<th>Cervical stenosis</th>
<th></th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (n = 10)</td>
<td>Absent (n = 154)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth (mm)</td>
<td>1.1 ± 0.7</td>
<td>0.8 ± 0.4</td>
<td>.008</td>
<td></td>
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<tr>
<td>Area (mm)</td>
<td>4.7 ± 3.1</td>
<td>2.9 ± 1.5</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Volume (mm)</td>
<td>6.6 ± 6.9</td>
<td>2.3 ± 1.8</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Additional endocervical excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 39)</td>
<td>7 (18)</td>
<td>32 (82)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>No (n = 125)</td>
<td>3 (2.4)</td>
<td>122 (98.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous loop excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 10)</td>
<td>4 (40)</td>
<td>6 (60)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>No (n = 154)</td>
<td>6 (4)</td>
<td>148 (96)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation.  
Data are given as mean ± standard deviation or n (%).
Consequences and Tx. Of Cx. Stenoses after Laser Conization or LEEP

255 women treated by laser conization and 277 by LEEP were regularly followed by postoperative colposcopy, for a mean period of 38 and 16 months, respectively.

Stenosis was defined as cervical narrowing which could not admit a 2.5 mm-diameter Hegar's dilator.

Stenosis complicated 10.2% of the laser conizations and 4.3% of the LEEP. Thus, 38 cases of cervical stenosis of which 7 were complete were diagnosed 2 to 40 months after treatment. Among the 34 non-menopausal women who developed a stenosis, 5 had a secondary amenorrhea, 6 a severe dysmenorrhea and one an infertility related to oligoamucorrhea. In the patients with stenosis, endocervical cell retrieval was possible in 21 (55%) cases and in none the squamocolumnar junction was visible at colposcopy. Seven patients underwent an enlargement plastic surgery of the cervical canal for incomplete stenosis and two a neostomia for complete stenosis. Cervical restenosis has been observed in 7 of 9 cases in a mean delay of 12 months (3 to 48 months). Nevertheless, the endocervical cell retrieval remained possible in 8 of 9 cases and after a mean follow-up of 26 months no menstrual troubles recurred.

LEEP provides fewer cervical stenosis than laser conization. The enlargement plastic surgery allows to correct durably the menstrual troubles in spite of the very frequent restenosis.

Service de Gynécologie Obstétrique I, Hôpital de Hautepierre, Hôpitaux Universitaires, Strasbourg.
**Gelsemiumium for Rigid (stenotic?) Os**

- Os hard, thick, rigid and undilatable
  - Homeopathy for Birthing, Jana Shiloh, M.A
- Os – rigid, thick, swollen Cervix – soft, flabby or spasmodically contracted into hard unyeilding ring
  - Table 3.2 Failure to Progress, Homeopathy for Midwives, Barbara Geraughty
- OS UTERI during labor; state of: (Delivery, during) rigid: **Caul. Cham. Gels.**
  - SYNTHEISIS Repertorium Homeopathicum Syntheticum, Dr. Frederik Schroyens
- Genetalia, Female, Rigidity of os during labor: **Caul., Cham., Gels.**
  - Repertory of the Homoeopathic Materia Medica: Kent’s Repertory, J.T. Kent
• RESULTS: Five hundred ninety-eight women with prior LEEP, 588 women with screening cytology only, and 552 women with cervical biopsy were included in this study. (Notice no conizations)

• After adjusting for relevant confounders, similar rates of cesarean delivery were seen in women with prior LEEP (31.6%) and women with prior cervical cytology only (29.3%, adjusted odds ratio [OR] 1.06, 95% confidence interval [CI] 0.79–1.41).

• Likewise, no differences were found in rates of cesarean delivery when women with prior LEEP were compared with those with a prior punch biopsy (29.0%, adjusted OR 0.99, 95% CI 0.74–1.33).

• Among women who had a cesarean delivery, arrest of labor was the indication for cesarean delivery in a similar proportion of women in the groups (LEEP compared with cytology only, P=.12; LEEP compared with biopsy, P=.50)

• Loop electrosurgical excision procedure specimen size did not vary by delivery mode. Length of time between LEEP and subsequent pregnancy also did not influence delivery mode.
Hard Stop on Elective Inductions Earlier than 39 weeks gestation

- The majority [of hospitals], 67%, have a formal policy against non medically indicated labor induction, and among those without a formal policy, just over half said it was against their standard of care.

- Comparing 9515 before and 2641 after “hard stop” policy outcomes:
  - Significant decrease of 5.9 hours median time to delivery (P=.002)
  - C/S rate for elective inductions from 15 to 7% (P=.05)
  - NICU admissions down 1/3 from 3% to 2% (p=.02)
  - No increase in the stillbirth rate.

The “Delightful Surprise” outcomes of such a crazy policy...

- "Something we didn't even anticipate as a benefit of this policy, but was a delightful surprise to see, was a decreased admission rate to the neonatal intensive care unit," Dr. Healy told Medscape Medical News at the meeting.

- "You have less of the early term admissions for things that are not life-threatening, but still disruptive of the neonatal period that will affect breast-feeding and maternal-neonatal bonding," said Angela Silber, MD, director of maternal-fetal medicine at Summa Akron City Hospital, OH.

- His survey, presented here at the American Congress of Obstetricians and Gynecologists (ACOG) 61st Annual Clinical Meeting, found that nearly two thirds of more than 2600 hospitals are on the bandwagon.

- "And we're even considering stopping elective inductions completely — it's just a matter of time."

Vaginal Delivery Best, says ACOG guideline, March 2013

- Vaginal deliveries should be the norm and early cesarean deliveries should be avoided, according to ACOG guidelines published March 21 in Obstetrics & Gynecology.

- "In the absence of maternal or fetal indications for cesarean delivery, a plan for vaginal delivery is safe and appropriate," ACOG states, noting that fear of childbirth pain is not a valid reason for surgery.
C/S risks

- Although planned cesarean deliveries carry a lower chance of hemorrhage, they are also linked to risks for bladder and bowel injury, longer hospital stays, higher infection rates, and increased neonatal respiratory morbidity. Moreover, rates of postpartum pelvic pain, sexual dysfunction, pelvic organ prolapse, and depression — which some women hope to avoid via surgical delivery — remain unchanged.
- ACOG emphasizes that surgical delivery be especially avoided in women planning to have several children because subsequent cesarean deliveries are tied to increasing risks for complications, such as placenta previa or accreta, uterine rupture, and emergency hysterectomy.
There are some things that we don’t understand. Some of those things need studies to explain them. Some of them are apparent with application of some common sense. Others are just part of the Mystery of Being.

That being said, Let’s look at some studies.
The Virus: HPV

Nonenveloped double-stranded DNA virus

- >100 types identified\(^2\)
- 30–40 anogenital\(^2,3\)
  - 15–20 oncogenic\(^*,2,3\) types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58\(^4\)
    - HPV 16 (54%) and HPV 18 (13%) account for the majority of worldwide cervical cancers.\(^5\)
  - Nononcogenic\(^†\) types include: 6, 11, 40, 42, 43, 44, 54\(^4\)
    - HPV 6 and 11 are most often associated with external genital warts.\(^3\)

\(^*\)High risk; \(^†\)Low risk

> 100 HPV types

Mucosal
(~40 types)

“high-risk”
types
(16,18)

“low-risk”
types
(6,11)

• low/high grade cervical abnormalities
• anogenital cancers

Cutaneous
(~60 types)

Common
warts
(hands/feet)

• low grade cervical abnormalities
• genital warts
• recurrent respiratory papillomas

> 100 HPV types
General Organization of a Papillomavirus Genome*¹

*Bars represent open reading frames. E = early region; L = late region; bp = base pair

Cancer promotion by HPV

- **E5** Prevents cell differentiation

- **E6** Prevents cell differentiation; promotes p53 degradation (tumor suppressor gene)
  - Regulates cells’ entering apoptosis

- **E7** Prevents cell-growth arrest/differentiation; inhibits inhibitors of E2F transcription factor
  - mediating the expression of genes whose products are essential for inducing resting cells to enter the cell cycle and synthesize DNA
### Background: HPV associated conditions: HPV 16, 18, 6, 11

<table>
<thead>
<tr>
<th>HPV 16, 18</th>
<th>Estimated %</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cervical cancer</em></td>
<td>70%</td>
</tr>
<tr>
<td><em>High/low grade cervical abnormalities</em></td>
<td>30-50%</td>
</tr>
<tr>
<td><em>Anal, Vulvar, Vaginal, Penile</em></td>
<td>~</td>
</tr>
<tr>
<td><em>Head and neck cancers</em></td>
<td>~</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPV 6, 11</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Low grade cervical abnormalities</em></td>
<td>10%</td>
</tr>
<tr>
<td><em>Genital warts</em></td>
<td>90%</td>
</tr>
<tr>
<td><em>RRP (recurrent respiratory papillomatosis)</em></td>
<td>90%</td>
</tr>
</tbody>
</table>

Estimated Annual Incidence of Select HPV-Related Disease in the United States

- 9,710 new cases of cervical cancer
- 330,000 new cases of high-grade cervical dysplasia (CIN 2/3)
- 1.4 million new cases of low-grade cervical dysplasia (CIN 1)
- 1 million new cases of genital warts

Most Prevalent HPV Types in Cervical Adenocarcinoma

Risk Factors for HPV Infection

Women
- Young age (peak age group 20–24 years of age)¹
- Lifetime number of sex partners²
- Early age of first sexual intercourse³
- Male partner sexual behavior³
- Smoking⁴
- Oral contraceptive use⁴
- Uncircumcised male partners⁵

Men
- Young age (peak age group 25–29 years of age)¹
- Lifetime number of sex partners⁶
- Being uncircumcised⁶

Reducing the Risk of HPV Transmission

- Abstinence from genital contact$^{1,2}$
- Lifetime mutual monogamy$^{2,3}$
- If used correctly, condoms can help reduce the risk of HPV infection.$^{4}$
  - In a recent prospective study, the incidence of genital HPV infection was 37.8% patient-years at risk among women whose partners used condoms for all intercourse, as compared with 89.3% patient-years at risk in women whose partners used condoms less than 5% of the time.$^{4}$

Background- Cervical abnormalities

- Pap test: ASC-US, Low or High grade SIL
- Biopsy: Cervical Intraepithelial Neoplasias (CIN)

Cervical Intraepithelial Neoplasia: CIN
Biology of HPV Infection: Low-Grade Lesions

1–3

Normal Cervix

HPV Infection (CIN* 1/Condyloma)

* CIN = cervical intraepithelial neoplasia
Biology of HPV Infection: High-Grade Lesions \(^1\)–\(^3\)

*CIN = cervical intraepithelial neoplasia; ICC = invasive cervical cancer


HPV Evasion of Exposure to Immune System

- No infection or replication in antigen-presenting cells (APCs)\(^1\)
- Infected keratinocytes may be less susceptible than other infected cells to cytotoxic lymphocyte-mediated lysis.\(^2\)
  - Little tissue destruction associated with HPV\(^3\)
- No blood-borne phase of infection\(^1\)
- Limited and delayed expression of late viral capsid proteins\(^1,2\)

Immune Response to Cervical HPV Infection

- Slow and weak immune response occurs 6–12 months after viral infection.\(^1\)
- Antibody responses to HPV infection do not occur in all women.\(^1,2\)
  - In a study of 588 college women, ~40% developed no measurable antibody response against HPV 16, 18, and 6 within 18 months of incident infection.\(^2\)
- Less clear is whether antibodies against one HPV type protect against subsequent reinfection with the same or another closely related type.\(^3\)
- Some evidence for presence of immunologic memory to specific HPV types\(^4\)

Colposcopic Appearance of the Normal Cervix

Photo courtesy of Dr. J. Monsonego
CIN as Seen in Colposcopy

Colposcopy findings confirmed by histology

- CIN 1: Mild dysplasia; includes condyloma (anogenital warts)
- CIN 2: Moderate dysplasia
- CIN 3: Severe dysplasia; cancer in situ (CIS); FIGO Stage 0

Colposcopy: Invasive Cervical Squamous Cell Carcinoma and Cervical Adenocarcinoma

Invasive Cervical Squamous Cell Carcinoma

Cervical Adenocarcinoma

Photos courtesy of Dr. J. Monsonego
## FDA approved HPV vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Covers</th>
<th>Manufacturer</th>
<th>Approval date</th>
<th>Doses</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil</td>
<td>Quadrivalent 6, 11, 16, 18</td>
<td>Merck</td>
<td>June 2006</td>
<td>3</td>
<td>130/dose</td>
</tr>
<tr>
<td>Cervarix</td>
<td>Bivalent 16, 18 only</td>
<td>GlaxoSmithKline</td>
<td>October 2009</td>
<td>3</td>
<td>128/dose</td>
</tr>
</tbody>
</table>
In June 2006, the recommendation was made by the national Advisory Committee on Immunization Practices (ACIP) that routine vaccination is recommended for girls between ages 11 and 12, can be given to girls as young as 9, and it is now recommended for males as well (2013 update).

Since 2006, legislators in at least 41 states and D.C. have introduced legislation to require the vaccine, fund or educate the public about the HPV Vaccine and at least 21 states have enacted legislation, including Colorado, Indiana, Iowa, Louisiana, Maine, Maryland, Michigan, Minnesota, Missouri, Nevada, New Mexico, New York, North Carolina, North Dakota, Rhode Island, South Dakota, Texas, Utah, Virginia and Washington.
Table 1. Severity of qHPV Adverse Events Following Immunization in the United States by Age, Reported to VAERS June 1, 2006, Through December 31, 2008

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Death</th>
<th>Nonfatal Serious</th>
<th>Nonserious</th>
<th>Total, No.</th>
<th>Reporting Rate&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9</td>
<td>0</td>
<td>0</td>
<td>41</td>
<td>41</td>
<td>0.2</td>
</tr>
<tr>
<td>9-10</td>
<td>0</td>
<td>11</td>
<td>160</td>
<td>171</td>
<td>0.7</td>
</tr>
<tr>
<td>11-12</td>
<td>2</td>
<td>60</td>
<td>950</td>
<td>1012</td>
<td>4.4</td>
</tr>
<tr>
<td>13-17</td>
<td>9</td>
<td>332</td>
<td>4009</td>
<td>4350</td>
<td>18.9</td>
</tr>
<tr>
<td>18-26</td>
<td>9</td>
<td>262</td>
<td>3687</td>
<td>3958</td>
<td>17.2</td>
</tr>
<tr>
<td>&gt;26</td>
<td>0</td>
<td>16</td>
<td>258</td>
<td>274</td>
<td>9.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
<td>59</td>
<td>2547</td>
<td>2618</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>740</td>
<td>11652</td>
<td>12424</td>
<td>53.9</td>
</tr>
</tbody>
</table>

Abbreviations: AEFI, adverse event following immunization; qHPV, quadrivalent human papillomavirus recombinant vaccine; VAERS, Vaccine Adverse Event Reporting System.

<sup>a</sup>Reports per 100,000 doses distributed.
### Table 2. Most Common and Other Selected qHPV Adverse Events Following Immunization in the United States, Reported to VAERS June 1, 2006, Through December 31, 2008

<table>
<thead>
<tr>
<th>AEFI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Serious Adverse Events</th>
<th>Nonserious Events</th>
<th>qHPV Alone&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Total, No.</th>
<th>Reporting Rate&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope, syncope vasovagal</td>
<td>93 (5)</td>
<td>1803 (95)</td>
<td>1396 (74)</td>
<td>1896</td>
<td>8.2</td>
</tr>
<tr>
<td>Local reaction&lt;sup&gt;d&lt;/sup&gt;</td>
<td>41 (2)</td>
<td>1700 (98)</td>
<td>1338 (77)</td>
<td>1741</td>
<td>7.5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>96 (6)</td>
<td>1476 (94)</td>
<td>1147 (73)</td>
<td>1572</td>
<td>6.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>119 (10)</td>
<td>1045 (90)</td>
<td>908 (78)</td>
<td>1164</td>
<td>5.0</td>
</tr>
<tr>
<td>Headache</td>
<td>150 (16)</td>
<td>787 (84)</td>
<td>688 (73)</td>
<td>937</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypersensitivity reaction&lt;sup&gt;e&lt;/sup&gt;</td>
<td>47 (6)</td>
<td>678 (94)</td>
<td>582 (80)</td>
<td>725</td>
<td>3.1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>22 (4)</td>
<td>590 (96)</td>
<td>501 (82)</td>
<td>612</td>
<td>2.6</td>
</tr>
<tr>
<td>Venous thromboembolic event</td>
<td>39 (69)</td>
<td>17 (31)</td>
<td>55 (98)</td>
<td>56</td>
<td>0.2</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>19 (37)</td>
<td>32 (63)</td>
<td>45 (88)</td>
<td>51</td>
<td>0.2</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>31 (74)</td>
<td>11 (26)</td>
<td>25 (60)</td>
<td>42</td>
<td>0.2</td>
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<tr>
<td>Anaphylaxis</td>
<td>8 (29)</td>
<td>20 (71)</td>
<td>18 (64)</td>
<td>28</td>
<td>0.1</td>
</tr>
<tr>
<td>Death</td>
<td>32 (100)</td>
<td>0</td>
<td>23 (72)</td>
<td>32</td>
<td>0.1</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>10 (100)</td>
<td>0</td>
<td>10 (100)</td>
<td>10</td>
<td>0.04</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>9 (100)</td>
<td>0</td>
<td>9 (100)</td>
<td>9</td>
<td>0.04</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>2 (100)</td>
<td>0</td>
<td>2 (100)</td>
<td>2</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Abbreviations: AEFI, adverse event following immunization; qHPV, quadrivalent human papillomavirus recombinant vaccine; VAERS, Vaccine Adverse Event Reporting System.

<sup>a</sup> Using MedDRA terms. More than 1 code may be assigned to a single report.

<sup>b</sup> No other vaccine was coadministered.

<sup>c</sup> Reports per 100,000 doses distributed.

<sup>d</sup> Local injection site reaction MedDRA codes include injection site abscess, injection site abscess sterile, injection site atrophy, injection site cyst, injection site desquamation, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site necrosis, injection site nodule, injection site edema, and injection site pain.

<sup>e</sup> Hypersensitivity reaction MedDRA codes include anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, cross-sensitivity reaction, dermographism, hypersensitivity, urticaria, urticaria thermal, and urticaria vesicular.

From: **Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine**

Among the 12,424 AEFI reports, 772 (6.2%) were serious, including 32 reports of death, 20 of which had medical records, autopsy, or death certificates available for evaluation. Sources of serious VAERS reports included manufacturer (66%), patient/parent (11%), clinician (10%), state health clinic (1%), and “other” (12%).

The most frequent serious symptom/MedDRA preferred-term codes included 159 reports of headache (21%), 119 nausea (16%), 113 dizziness (15%), 102 vomiting (13%), 102 pyrexia (13%), 102 fatigue (13%), and 98 syncope (13%).

Medically important serious events included 8 reports of anaphylactic reaction (1%), 9 deep vein thrombosis (1.2%), 31 GBS (4%), 25 hypersensitivity (2.5%), 10 transverse myelitis (1.3%), 6 pancreatitis (0.8%), 14 pulmonary embolism (1.8%), 23 death (3%), 68 convulsion (8.8%), 30 urticaria (3.9%), and 9 autoimmune disorder (1.2%).
Dr. Diane Harper speaks out against the HPV vaccine she helped design and carry out Phase II and III safety and effectiveness studies for

"If we vaccinate 11 year olds and the protection doesn't last... we've put them at harm from side effects, small but real, for no benefit," says Dr. Harper. "The benefit to public health is nothing, there is no reduction in cervical cancers, they are just postponed, unless the protection lasts for at least 15 years, and over 70% of all sexually active females of all ages are vaccinated." She also says that enough serious side effects have been reported after Gardasil use that the vaccine could prove riskier than the cervical cancer it purports to prevent. Cervical cancer is usually entirely curable when detected early through normal Pap screenings.

CBS News / August 29, 2009
Dr. Scott Ratner and his wife, who's also a physician, expressed similar concerns as Dr. Harper in an interview with CBS News last year. One of their teenage daughters became severely ill after her first dose of Gardasil. Dr. Ratner says she'd have been better off getting cervical cancer than the vaccination. "My daughter went from a varsity lacrosse player at Choate to a chronically ill, steroid-dependent patient with autoimmune myofasciitis. I've had to ask myself why I let my eldest of three daughters get an unproven vaccine against a few strains of a nonlethal virus that can be dealt with in more effective ways."
“Previous surveys on hypothesized sexual activity changes after human papillomavirus (HPV) vaccination may be subject to self-response biases. To date, no studies measured clinical markers of sexual activity after HPV vaccination. This study evaluated sexual activity-related clinical outcomes after adolescent vaccination.”

11 to 12 year old girls were administered 3 doses of HPV vaccination
They were followed for “up to 3 years” or until they were 14-15 year old girls
The cohort included 1398 girls (493 vaccine-exposed; 905 vaccine-unexposed).
Risk of the composite outcome (any pregnancy/sexually transmitted infection testing or diagnosis or contraceptive counseling) was not significantly elevated in HPV vaccine-exposed girls relative to HPV vaccine-unexposed girls. Incidence rate difference for Chlamydia infection and pregnancy diagnoses indicating little clinically meaningful absolute risk differences.
HPV vaccination in the recommended ages was not associated with increased sexual activity-related outcome rates.

Sexual activity-related outcomes after human papillomavirus vaccination of 11- to 12-year-olds.
Sexual Behavior among adolescent and young women...Demographics

- In 2007-2008, a total of 1243 girls/women aged 15-24 years responded to questions about receiving HPV vaccine.
- HPV vaccine initiation was higher among those aged 15-19 years than those aged 20-24 years (p<0.001). No differences existed by race/ethnicity for those aged 15-19 years, but among women aged 20-24 years, non-Hispanic blacks were less likely than non-Hispanic whites to have received the HPV vaccine (AOR=0.15). HPV vaccine initiation was greater for those with insurance regardless of age. HPV vaccination was not associated with being sexually active or number of sex partners at either age.
- Among sexually active adolescents aged 15-19 years, those who received HPV vaccine were more likely to always wear a condom (AOR=3.0).
- This study highlights disparities in HPV vaccine initiation by insurance status among girls/women aged 15-24 years and by race/ethnicity among women aged >19 years. No association was found between HPV vaccination and risky sexual behavior.

Human papillomavirus vaccine and sexual behavior among adolescent and young women. Liddon NC, Leichliter JS, Markowitz LE.
What once was the gold standard is rapidly becoming only red ribbon

Thanks to Dr. Sara Thyr, ND for forwarding this gem...initially detected at a bluegrass festival
Cervical Cancer Screening Guidelines for Average-Risk Women

<table>
<thead>
<tr>
<th>When to Start Screening</th>
<th>American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) 2</th>
<th>U.S. Preventive Services Task Force (USPSTF) 3</th>
<th>American College of Obstetricians and Gynecologists (ACOG) 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 21; Women aged &lt;21 years should not be screened regardless of the age of sexual initiation or other risk factors, (Strong recommendation)</td>
<td>Age 21. (A recommendation) Recommend against screening women aged &lt;21 years. (D recommendation)</td>
<td>Age 21 regardless of the age of onset of sexual activity. Women aged &lt;21 years should not be screened regardless of age at sexual initiation and other behavior-related risk factors. (Level A evidence)</td>
<td></td>
</tr>
</tbody>
</table>

Statement about annual screening

Women of any age should not be screened annually by any screening method. (Strong recommendation)

Individuals and clinicians can use the annual Pap test screening visit as an opportunity to discuss other health protection and preventive measures. Individuals, clinicians, and health systems should seek effective ways to facilitate the receipt of recommended preventive services at intervals that are beneficial to the patient. Efforts also should be made to ensure that individuals are able to seek care for additional health concerns as they present.

When to stop screening

Aged >65 years with adequate screening history. (D recommendation)

Aged >65 years with adequate screening history. (Level A evidence)

Screening post-hysterectomy

Women who have had a total hysterectomy (removal of the uterus and cervix) should stop screening. (D recommendation)

Recommend against screening in women who have had a hysterectomy (removal of the cervix). (D recommendation)

Woman who have had a hysterectomy (removal of the cervix) should stop screening and not restart for any reason. (Level A evidence)

The need for a bimanual pelvic exam

Not addressed in 2012 guidelines but was addressed in 2002 ACS guidelines. (D recommendation)

Addressed in USPSTF ovarian cancer screening recommendations (draft). (D recommendation)

Addressed in 2012 well-woman visit recommendations. Aged <21 years, no evidence supports the routine internal examination of the healthy, asymptomatic patient. An "extension-only" gynecal examination is acceptable. Aged 21 or older, no evidence supports or refutes the annual pelvic examination or speculum and bimanual examination. The decision on whether or not to perform a complete pelvic examination should be shared after a discussion between the patient and her health care provider. Annual examination of the external genitals should continue.

Screening among those immunized against HPV 16/18

Women at any age with a history of HPV vaccination should be screened according to the age specific recommendations for the general population.

The possibility that vaccination might reduce the need for screening with cytology alone or in combination with HPV testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened.

Women who have received the HPV vaccine should be screened according to the same guidelines as women who have not been vaccinated. (Level B evidence)
Simple screening guidelines
Made simple.

- Do not screen before 21 regardless of sexual activity
- Start at 21 regardless of sexual activity or immunization
- DO NOT screen annually (but still schedule annual well-woman visits)
- Bimanual exam only if symptomatic, continue with external genital examination. (ACOG)

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;21</th>
<th>21-29</th>
<th>30-65</th>
<th>&gt;65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap screen</td>
<td>Never</td>
<td>Every 3 years Regardless of sexual activity</td>
<td>Every 3 years Regardless of sexual activity</td>
<td>Stop with adequate Screening hx.</td>
</tr>
<tr>
<td>HPV</td>
<td>Never</td>
<td>Never</td>
<td>Every 5 years</td>
<td>Stop with adequate Screening hx.</td>
</tr>
</tbody>
</table>
Committee on gynecologic practice, the American College of Obstetricians and Gynecologists.
Progression likelihood and timeline

- Approximately 57% of low-grade lesions (CIN 1) will regress, 32% will persist, and 11% will progress. The risk of developing invasive cancer is estimated to be 1% in patients with CIN 1.
- Approximately 43% of CIN 2 lesions will regress, 35% will persist, 22% will progress to CIN 3, and 5% will progress to invasive cancer.
- The likelihood of CIN 3 regressing is about 32%, persistence is <56%, and rate of progression to invasive cancer is >12%.
- In studies of women with HPV infection who developed CIN 2 or 3, the initial abnormal smear was interpreted as CIN 2 or 3 in two thirds of cases, indicating that most CIN 3 lesions do not evolve from CIN 1.
- In a large, prospective study, mean times of progression from mild, moderate, or severe dysplasia to development of carcinoma in situ (CIS) were 58, 38, and 12 months, respectively.
## Progression likelihood and timeline

<table>
<thead>
<tr>
<th></th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression</th>
<th>Mean interval Progression to CIS</th>
<th>Mean Risk of developing CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CIN I</strong></td>
<td>57 %</td>
<td>32 %</td>
<td>11 %</td>
<td>58 months 4 years 10 mo</td>
<td>1 %</td>
</tr>
<tr>
<td><strong>CIN II</strong></td>
<td>43 %</td>
<td>25 %</td>
<td>22 %</td>
<td>38 months 3 years 2 mo</td>
<td>5 %</td>
</tr>
<tr>
<td><strong>CIN III</strong></td>
<td>32 %</td>
<td>56 %</td>
<td>12 %</td>
<td>12 One year</td>
<td>12 %</td>
</tr>
</tbody>
</table>
Varieties of the Healthy Cervix

Nulliparous cervix with SCJ close to os

Cervical ectropion

Parous cervix with SCJ further from os.

Nabothian cysts.
The Cervical Transformation Zone

- Area of immature metaplasia between the original and current squamocolumnar junction (SCJ)
- ~99% of HPV-related genital cancers arise within the transformation zone of the cervix
- The Pap test is used to obtain cells from the cervix (primarily transformation zone) for cervical cytology screening.

Anatomy of Cervical Tissues

- **Squamous Epithelium**
- **Columnar Epithelium**
- **Transformation Zone**

Key Features:
- Original (native) squamocolumnar junction
- Transformation zone
- New squamocolumnar junction
- Original (native) squamous epithelium
- Metaplastic squamous epithelium
- Columnar epithelium
- External os
The Squamocolumnar Junction (SCJ)

Birth to prepuberty

Menarche to early reproductive age

Mid-reproductive age/30s

Perimenopause

Postmenopause
A simple screening technique using an inexpensive agent dramatically reduced deaths related to cervical cancer in a population of Indian women. Visual inspection with acetic acid or vinegar (VIA), conducted by nonmedical personnel trained to deliver basic healthcare, cut the death rate by 31%.

"It consists of an application of 4% vinegar to the cervix, and the results are available in 1 minute," Dr. Shastri explained. "Paramedical workers can be trained in 4 weeks."

World-wide locations of IARC’s screening initiatives in collaboration with national institutions for the prevention and early detection of cervical, oral and/or breast cancers.


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Visual Inspection with Acetic Acid (VIA)

**STRENGTHS**
- May be performed during menses, in the presence of STIs or vaginal infections, during pregnancy, at postpartum exams, or post-abortion
- Offers immediate results
- Cheap

**LIMITATIONS**
- Ineffective when SCJ is not visible (i.e. peri- or post-menopause)
- Because endocervix cannot be visualized, poor at detecting glandular cell abnormalities that develop in the endocervix
Visual Inspection with Acetic Acid (VIA)

**Protocol**

1. Perform speculum exam.
2. Visualize the cervix.
3. Identify SCJ and TZ.
4. Apply a 4-5% acetic acid solution to cervix using a saturated cotton ball or swab. Wait 60 seconds.
5. Check TZ/SCJ for acetowhite areas.
6. Repeat gently if results are indeterminate.
7. Absorb excess acetic acid.
8. Chart and explain results.

VIA Negative

VIA Positive
VIA- or VIA+ ?

1. 
2. 
3. 
4. 
5. 
6.
VIA- or VIA+?

1. VIA +
2. VIA -
3. VIA -
4. VIA +
5. VIA +

Suspicious for cancer
6. VIA +
OK, so, if NOT the Vaccines... and not so much the Paps...

- Then what do we as Naturopathic Physicians have to offer that fall under that aforementioned category of “more effective ways”?
Green tea has recently been shown to influence numerous mechanisms which are favorable towards preventing and/or treating HPV related lesions. Epigallocatechin-3-gallate has been shown to inhibit epidermal growth factor receptor (EGFR) signaling pathway. EGFR activation is required for cervical cell proliferation which suggests agents which inhibit EGFR may be of important therapeutic value in prevention and treatment of cervical dysplasia and genital warts. Two other in vitro studies demonstrated EGCG inhibits the growth of human cervical cancer cell lines, induces apoptosis, inhibits telomerase activity in cervical cell lines and has a role in regulation of gene expression.

Overall, 35 of 51 (69%) response rate was noted for the green tea products compared with a 10% response rate in the untreated controls. The mechanisms involved appear to be apoptosis, cell cycle arrest, modification of gene expression and anti-tumor effects, specifically, inhibition of cell proliferation. These results demonstrate green tea extracts in the form of a vaginal delivery and an oral capsule are effective strategies for treating cervical lesions.

Cervical-Vaginal Flora

The cervical-vaginal flora of 21 women with invasive cervical cancer was determined. The cultures yielded polymicrobial growth with anaerobic organisms predominating. As compared with other studies of vaginal flora, the cancer patients were found to have a decreased frequency of isolation of aerobic lactobacilli, Staphylococcus epidermidis. and enterococci, and an increased frequency of isolation of Escherichia coli and Bacteriodes species. The composition of the anaerobic vaginal flora in these patients is similar to that described for immunosuppressed renal transplant patients.

Cervical-Vaginal Flora of Women With Invasive Cervical Cancer
BV + HPV = CIN?

- Bacterial vaginosis, is associated with a 357% increase in the incidence of cervical intraepithelial neoplasia (CIN), an abnormality of cervical cells that may lead to cervical cancer.

- In a retrospective evaluation of Pap smears obtained in 6,150 women, bacterial vaginosis was diagnosed, by detection of clue cells in Pap smears, in 617 (10%) of the patients. Cervical intraepithelial neoplasia was found in 5% of these women with vaginosis, as compared with 1.4% of the women without vaginosis. Moreover, when early-stage CIN was excluded, second- and third-stage CIN occurred in 2.9% of the patients with bacterial vaginosis but in only .4% of those without this infection.

Dr. Jens Platz-Christensen and colleagues at Sahlgrenska University Hospital in Goteborg, Sweden, *Acta Obstetricia et Gynecologica Scandinavica* reprinted in Oncology, vol. 1 no. 4, April 1995
"The possibility exists that bacterial vaginosis is in some way associated with the development of cervical intraepithelial neoplasia," the authors conclude, noting that bacterial vaginosis may be a cofactor to the potentially cancer-causing human papillomavirus (HPV).

The association between HPV and the development of CIN and cervical cancer is well documented. The abnormal vaginal flora in bacterial vaginosis can produce nitrosamines. These carcinogens may act synergistically with HPV to damage epithelial cells, thus aiding in the development of CIN.

Dr. Jens Platz-Christensen and colleagues at Sahlgrenska University Hospital in Goteborg, Sweden, reported in Oncology, vol. 1 no. 4, April 1995
Do not apply to the cervix...

- **Hot Peppers**
  - Spice up your diet with some jalapenos and chili peppers. The ingredient that gives these vegetables their kick, capsaicin, has been shown to also help prevent cancer. It can **neutralize nitrosamines, which cause cancer**. Capsaicin is especially effective in helping to prevent stomach cancer.

Lactobacillus/Honey suppositories for Cervical Health?

- A study in 1937 reported the success of using special glucose tablets in the treatment of gonorrheal vulvovaginitis. Shockingly, doctors have known for decades that glycogen in the squamous mucosa of the cervix and vagina is depleted in cases of cervical cancer.

- Fructooligosaccharides and glucooligosaccharides are found in a wide variety of foods, and research indicates they are found together in the most perfect of natural prebiotics, honey. Like glycogen, honey is a hydrophilic molecule, which means it draws water into cells, naturally moisturizing tissues. It feeds the most beneficial microorganisms so they multiply quickly and crowd out vaginal pathogens.

---

The Cervical Escharotic Treatment: Day of Treatment Materials
Setting up before you start!

Open three bromelain capsules into sterile urine cup labeled with client’s initials and “Brom”

Pour at least 1 Tb. Calendula Succus into urine cup labeled with initials and “CS”

Measure out ¼ tsp Zn/Cl and ¾ tsp. Sanguinaria tincture, combine in urine cup labeled with initials and “Zn/Cl/Sang.”
E Tx. Tricks that help: The Bromelain powder “poofer”
Locate and clean the cervix with calendula succus or distilled water
Bromelain Pipette fill
The Bromelain “Poof”
(It’s all in the thenar eminence)
Second Try, sideways, fast...
Apply bromelain powder “poof” or drizzle the bromelain “slurry”

To the face of the cervix
To the endocervical canal
Too close, ouch, too warm!

OK, That’s better, Just warm. 15 minutes
Visualization/Guided Imagery
Zn/Cl and Sanguinaria: 1 Minute

To the face of the cervix

To the endocervical canal
Adding the Vag Pak Suppositories

Lay them into the speculum first

Then tip them up to lay against the cervix
The Grand Finale:
(also known as the other tricky part)
Practical Matters:

- Schedule each E tx. twice per week for 3-5 weeks
  - With at least 2 days between treatments
  - So, in office time, that usually means Monday & Thursday OR Tuesday and Friday
- Think ahead about office hours, when menstrual cycle is due, client’s meetings, holidays, school performances,
- Consider rescheduling complications...snow days, emergencies

Billing: total materials/supplement cost Plus:

- Number of visits/treatments (discount office visit rate for 6-10 scheduled visits in the series?)
- Add these and break up the cost over the whole time, or have session fully paid by the first treatment
Other Matters to consider

• History of Abuse
• Pelvic Rest: No intercourse during the duration of the treatment
• Need to be able to go home and rest after treatment: movie night, not bowling night... especially as treatments progress
• Panty liners (as Vag Pak will stain clothing)
• Vaso vagal response to cervical disturbances in some people, be sure client sits for a few minutes before jumping into the car
Post E tx. treatment regimen

- After the 3-5 weeks of E tx. (according to extent and type of HPV being treated), the recommendations are for 12 weeks (3 mos.):
  - continued suppositories 6 d/week
  - Diet to remain vegetarian/vegan
  - Systemic tinctures
  - Systemic nutrients
Follow up testing/visits

- Pap re-testing in 3-6 months
- HPV testing
- Consider VIA
- Consider testing vaginal flora periodically
- Consider testing/vigilance regarding BV
Feel free to contact with questions

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