

# Management of Cervical Dysplasia and Human Papillomavirus

by Marianne Marchese, ND

In the 1950s, George Papanicolaou and Herbert Traut developed a test to screen for cervical cancer in women, called the Pap smear. At the time, cervical cancer was the leading cause of death in women in the US; now it ranks only 13th. Thanks to the Pap test, precancerous lesions called dysplasia are diagnosed more frequently than invasive cervical cancer. Annual screening and early diagnosis give physicians a chance to start treatment and prevent cervical cancer.

Some risk factors for cervical cancer include<sup>1</sup>:

- multiple sexual partners
- young age at first intercourse (< 16)
- intercourse with uncircumcised partner
- unprotected intercourse
- human papillomavirus (most commonly strains 16, 18, 45, 31, and 33)
- chlamydia and HIV
- compromised immune system
- smoking
- poor nutritional status
- diethylstilbestrol (DES) exposure
- long-term oral contraceptive use (> 5 years)
- low socioeconomic status
- lack of access to health care or health insurance
- rural residence

The main risk factor for cervical cancer is the presence of human papillomavirus (HPV) infection. It is estimated that cervical infection with one of 16 HPV types accounts for all cervical cancers.<sup>2</sup> HPV type 16 is the most common carcinogen detected in women with cervical cell changes including precancerous and cancerous lesions. HPV type 18 is the second most common type found in

women with cervical cancer as well as adenocarcinomas. The other HPV types implicated in cervical cancer are 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82.<sup>2</sup> These, along with 16 and 18, are called high-risk HPV types. Types 6 and 11, which cause genital warts, are considered low risk because they are not linked to cervical cancer.

It is important to screen women for high-risk HPV along with their annual Pap smear, which screens for cervical cell abnormalities. HPV testing can be performed during the Pap smear. Most Pap smear testing is now done with liquid-based cytology using the ThinPrep or SurePath vials, which can test for both abnormal cervical cells and HPV. There is also a separate swab test for HPV, called the Digene probe.

In December 2009, the American College of Obstetricians and Gynecologists (ACOG) made the following recommendations in regard to screening women for cervical cell changes and HPV<sup>3</sup>:

1. Women ages 21 to 30 will be screened every two years instead of every year, using the slide Pap or liquid-based cytology.
2. Women age 30 and older who have had three consecutive negative cervical cytology test results and who have no history of moderate cervical dysplasia (CIN 2) or severe cervical dysplasia (CIN 3), are not HIV-infected, are not immunocompromised, and were not exposed to DES in utero may be screened once every three years with either the slide Pap or liquid-based cytology.

3. Women of any age with certain risk factors may need more frequent screening, including those who have HIV; are immunosuppressed; were exposed to DES in utero; and have been treated for cervical intraepithelial neoplasia (CIN) 2, CIN 3, or cervical cancer.
4. Women over age 30 should have both cervical cytology and high-risk HPV testing. This is referred to as combination testing.
5. Women under 30 should be tested for high-risk HPV if the Pap comes back as atypical cells of undetermined significance (ASC-US). This is called reflex testing and can be done from the same sample if liquid-based cytology is done. Any Pap abnormality showing greater than ASC-US is presumed to have high-risk HPV.
6. It is acceptable to discontinue cervical cancer screening between 65 and 70 years of age in women who have three or more negative cytology test results in a row and no abnormal test results in the past 10 years.

In the past, ACOG recommended that cervical screening begin three years after first sexual intercourse or by age 21, whichever occurred first. Moving the baseline cervical screening to age 21 avoids unnecessary treatment of adolescents. Although the rate of HPV infection is high among sexually active adolescents, invasive cervical cancer is very rare. The immune system clears the HPV infection within one to two years among most adolescent women. The large majority of cervical dysplasia in adolescents resolves on its own without treatment.

## The PAP Came Back Abnormal – Now What?

A cervical cell screening could come back with several abnormalities:

- ASC-US (atypical squamous cells of undetermined significance)
- ASC-H (atypical squamous cells, cannot exclude HSIL)
- LSIL (low-grade squamous epithelial lesions)
- HSIL (high-grade squamous epithelial lesions)

In September 2006, 146 experts from 29 organizations met to develop guidelines for conventional medicine management of women with abnormal cervical cancer screenings. Here are the highlights from that meeting<sup>4</sup>:

- cytology and HPV negative: rescreen at 3 years
- cytology negative, HPV positive: watch and wait and repeat both in 6 months
- cytology ASC-US, HPV negative: watch and wait and repeat 1 year
- cytology ASC-US, HPV positive: refer directly for colposcopy
- cytology > ASC-US and any HPV: refer directly for colposcopy

In adolescents with ASC-US and HPV positive or with LSIL, it is now recommended to watch and wait, and repeat the Pap in one year. Only adolescents with HSIL or above should be referred directly to colposcopy. If a woman is pregnant and has a Pap that comes back with ASC-US and she is over 25, then the management is identical as for nonpregnant women. It is acceptable to defer colposcopy until 6 weeks postpartum, and endocervical sampling and endocervical curettage are, of course, unacceptable in pregnant women.<sup>4</sup>

If the Pap comes back showing atypical glandular cells (AGC), these are typically caused by a benign condition such as polyps or reactive cellular changes. However, AGC can be associated with underlying adenocarcinomas of the cervix, uterus, and ovary.

The recommended follow-up for AGCs includes<sup>4</sup>:

- colposcopy with endocervical sampling

- endometrial sampling if the woman is > 35 or < 35 with abnormal bleeding
- atypical endocervical or endometrial cells present on Pap, then do an endometrial biopsy
- HPV testing

You can download algorithms of conventional practice management guidelines at website of the American Society for Colposcopy and Cervical Pathology (ASCCP), [ASCCP.org](http://ASCCP.org).

## What Happens After Colposcopy?

During a colposcopy exam, a biopsy may be taken at the site of the cervical cell abnormality, as well as a sample of cells from endocervical canal. Endocervical canal sampling is known as endocervical curettage. Abnormalities seen on biopsied tissue can include:

- cervical intraepithelial neoplasia
- CIN I = mild dysplasia (low grade)
- CIN II = moderate dysplasia (high grade)

- CIN III = severe dysplasia or (high grade)
- carcinoma in situ (high grade)

The ASCCP has determined guidelines for conventional management of cervical intraepithelial neoplasia or adenocarcinoma in situ. They include<sup>5</sup>:

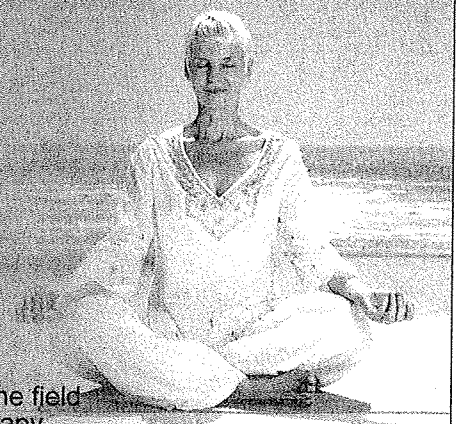
- CIN I and satisfactory colposcopy: follow up without treatment with PAP and HPV test at 6 months. If still positive, repeat the colposcopy. Alternative approach is to follow up at 12 months with repeat colposcopy. A third approach is to treat immediately with cryotherapy or a LEEP (loop electrosurgical excision procedure);
- CIN I and unsatisfactory colposcopy: diagnostic excisional procedure (cone biopsy);
- CIN II and III with satisfactory colposcopy: LEEP or diagnostic excisional procedure;
- CIN II and II with unsatisfactory colposcopy: diagnostic excisional procedure (cone biopsy).

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## Cervical Dysplasia and HPV

### There Are Options

Naturopathic physicians offer an alternative approach to managing both abnormal Pap results and cervical epithelial neoplasia. Addressing the cause is key to treating the disease. This begins by educating the patient on practicing safe sex to decrease transmission of HPV, HIV, and other sexually transmitted diseases. Smoking is linked to cervical cancer, as it increases the duration of infection with high-risk HPV.<sup>6</sup> It also weakens the immune system. Smoking cessation and immune system support are an important part of treatment for cervical dysplasia. Poor nutritional status is linked to cervical cancer. Folate and B12 deficiency has been associated with increased HPV infection.<sup>7</sup> Low serum retinol levels have been linked to increased risk of cervical epithelial neoplasia.<sup>8</sup> A comprehensive nutritional intake and dietary counseling should be included in treatment.

### No Need to Watch and Wait

When the Pap comes back with ASC-US and no HPV, normal cytology with HPV present, or ASC-US with HPV in younger women, conventional medicine suggests to watch, wait, and repeat the Pap. This is where naturopathic medicine would begin treatment. Supporting the immune system to fight off HPV, as well as treating HPV directly, can reverse the low-grade cervical cell abnormality and eliminate HPV. Guidelines for referral to colposcopy are the same.

Naturopathic medicine can also treat cervical intraepithelial neoplasia I and II. This treatment consists of oral systemic support as well as local cervical treatments.

Some important herbal medicines and nutrients for systemic treatment include:

**Folic acid:** There have been several studies showing that low serum folate levels are linked to cervical dysplasia and high folate blood levels to the

prevention of CIN I.<sup>9,10</sup> Improvement in cervical dysplasia using folic acid supplementation is also well documented.<sup>11</sup> The doses vary and are most often given with vitamin B12 as not to mask B12 anemia.

**Indole-3-Carbinol:** Indole-3-carbinol (I3C) is present in all members of the cruciferous vegetable family, including cabbage, broccoli, brussels sprouts, cauliflower, and kale. Studies indicate that I3C has the potential to prevent and even treat a number of common cancers, especially those that are estrogen related.<sup>12</sup> In a double-blind, placebo-controlled study, 30 patients with biopsy-confirmed CIN II-III were randomized to receive placebo or 200 or 400 mg oral I3C daily for 12 weeks. Three patients did not complete the study. None of the 10 patients in the placebo group had complete regression of CIN. Four of eight patients in the 200 mg/day group and four of nine in the 400 mg/day group had complete regression of CIN.<sup>13</sup> I3C is easily available over the counter as a supplement or simply by eating 4 to 5 servings of cruciferous vegetables a day.

**Antioxidants:** Antioxidants are known for their cancer-prevention properties. Studies have linked antioxidant levels to CIN and cervical cancer. In one study, blood levels of coenzyme Q10 (CoQ10) and vitamin E were measured in patients with biopsy-confirmed CIN, cervical cancer, and normal PAP smears (controls). Results showed that levels of CoQ10 and vitamin E were significantly lower in patients with diagnosed CIN and cervical cancer when compared with controls.<sup>14</sup> Levels of CoQ10 from cervicovaginal epithelial cells were measurable and also appeared to be significantly lower in women diagnosed with CIN.<sup>15</sup> These findings suggest that low levels of these two antioxidants may play a role in the pathogenesis of cervical dysplasia.

**Vitamin C:** Vitamin C is an excellent antioxidant that boosts

the immune system and has proven anticancer effects. It is known that women with cervical dysplasia have low blood levels of vitamin C.<sup>16</sup> A recent study showed that women with high intake of dietary vitamin C had a reduction in the risk of cervical dysplasia.<sup>17</sup> A study on Korean women looked at 58 colposcopy-confirmed cases of CIN and compared them with 86 women with normal Pap smears. The plasma concentration of vitamin C was significantly lower in the CIN group than in the control group.<sup>18</sup> This suggests a role for vitamin C in the treatment of cervical dysplasia.

**Green Tea Extract:** Epigallocatechin-3-gallate (EGCG) is the standardized extract from green tea. It is known to inhibit epidermal growth factor receptor, which is needed for cervical cell growth. A recent study looked at 51 women with HPV-infected cervical lesions divided into 4 groups and compared them with 39 controls. Green tea ointment was applied locally to 27 patients twice a week. For oral delivery, a EGCG capsule was taken every day for 8 to 12 weeks. In the study, 20 out of 27 patients under ointment therapy showed a response. Six out of eight patients under green tea ointment plus capsule therapy showed a response. Six out of 10 patients under EGCG capsule therapy showed a response. Overall, a 69% response rate was noted for treatment with green tea extracts, as compared with a 10% response rate in untreated controls. A good response meant an improvement in cervical dysplasia.<sup>19</sup>

**Coriolus Versicolor:** *Coriolus* is a mushroom commonly used in Asian cultures for its immune properties. It is often called an immunomodulator and has been studied for its immune-enhancing properties in cancer patients undergoing chemotherapy. Recently, it has been studied for its immunomodulating effects on HPV and reversing early stages of cervical cancer.<sup>20</sup> A study published in the *Townsend Letter* (November 2006) by J. Silva Couto looked at women with cervical dysplasia, LSIL (CIN I and HPV). Half of the women in the LSIL

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group were given 3g/day of *Coriolus* a day for one year and the other half took none. Silva Couto found that *Coriolus versicolor* supplementation over a period of one year substantially increased regression of the dysplasia (LSIL) and induced clearance of the high-risk subtypes of the HPV virus. Some interesting findings of the study include the following:

- *Coriolus versicolor* supplementation demonstrated a 72% regression rate in LSIL lesions compared with 47.5% without supplementation.
- *Coriolus versicolor* supplementation demonstrated a 90% regression rate in the high-risk HPV virus subtypes compared with 8.5% without supplementation.

Local treatments applied to the cervix include:

**Escharotic Treatment:** The use of escharotic or caustic treatments for epithelial cancers is based on a centuries-old observation that select plant and mineral extracts could be used to treat topical skin lesions.

Two small studies show the efficacy of this treatment in reversing cervical dysplasia in women.<sup>21,22</sup> This treatment is used for CIN I and II after a satisfactory colposcopy is performed and if there is no disease in the endocervical canal and no glandular cells are present. Escharotic treatment for cervical dysplasia involves the local application of a natural enzyme, bromelain, to the surface of the cervix. This is left in place for 15 minutes with heat applied to activate the enzyme. The proteolytic properties in bromelain dissolve the top layer of cells on the cervix that are infected and damaged by the HPV virus. A mixture of zinc chloride and the plant *Sanguinaria canadensis* is applied to the cervix to cause sloughing of abnormal tissue. Zinc chloride is caustic and disrupts the cellular membrane integrity and the mucus overcoating to allow the *Sanguinaria* to penetrate the cells. *Sanguinaria* has been shown to have antineoplastic qualities.<sup>21</sup> The treatment is performed twice per week with at least two days in between treatments for 4 to 5 weeks. The ZnCl solution is made

by a compounding pharmacist. Often a Vag Pack suppository is used after each treatment

**Vag Pack Suppository:** Vaginal depletion packs have been in use since the 1800s. The substances within the packs draw infection out of the cervical cells and boost the immune system. Each suppository contains magnesium sulfate, glycerin complex, hydrastis tincture, thuja oil, tea tree oil, bitter orange oil, vitamin A (as palmitate) 100,000 IU, ferric sulfate, and ferrous sulfate in polybase. *Hydrastis canadensis* is effective against many microbial pathogens, as are the essential oils of tea tree, thuja, and bitter orange. Vag Pack suppositories are often used for mild dysplasia and/or high-risk HPV.

### Summary of Naturopathic Treatment Options

1. education on safe sex practices
2. smoking cessation program
3. nutritional counseling and diet plan
4. support for the immune system
5. systemic treatment
  - a. folic acid 5–10 mg day
  - b. B12 1,000 mcg day
  - c. indole-3-carbinol 400 mg day
  - d. antioxidants
  - e. vitamin C 3–4 g day
  - f. green tea extract 1,500 mg day
  - g. *coriolus versicolor* 3,000 mg day
6. Local cervical treatment
  - a. escharotic treatment
  - b. Vag Pack suppository

### Notes

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