Gynecologic Cancer Tied To Lynch Syndrome Risk

BY JANE SALODOF MACNEIL
Senior Editor

SAN DIEGO — More attention needs to be paid to the risk of hereditary colorectal cancer in women diagnosed with endometrial and ovarian cancers—and vice versa, according to studies reported at the annual meeting of the Society of Gynecologic Oncologists.

Investigators from the University of Alabama, Birmingham, urged that all endometrial cancer patients younger than 50 years be screened for hereditary nonpolyposis colorectal cancer (HNPCC) mutations.

Another group, from the Roswell Park Cancer Institute in Buffalo, N.Y., recommended that HNPCC, also known as Lynch syndrome, be considered when evaluating patients who have a family history of ovarian cancer but do not screen positive for BRCA gene mutations.

For women diagnosed with HNPCC, researchers at the University of California, San Francisco, reported that prophylactic hysterectomy with bilateral salpingo-oophorectomy would be more cost effective than annual screenings or medical examinations for gynecologic cancers.

Lynch syndrome conveys lifetime risks of 60%-80% for colon cancer, 40%-60% for endometrial cancer, and 10%-20% for ovarian cancer in women, according to Dr. Lee-May Chen, who led the California project. Although endometrial cancer is more common, she said it is usually more treatable than ovarian cancer because endometrial bleeding leads to earlier detection.

Most women known to have HNPCC are screened by colonoscopy every year or two, Dr. Chen added, but tests for gynecologic cancers are not as effective or as routine.

The Alabama investigators, in looking for HNPCC in endometrial cancer patients, used immunohistochemical staining to screen pathologic specimens from 61 women younger than 50 years who were diagnosed between 1996 and 2006. They found mutations associated with HNPCC in 21 women (34%), of whom 5 had multiple mutations.

"The rate of HNPCC in this population is considerably higher than previous reports. These women, once diagnosed [with HNPCC], can benefit from further screening," said Dr. Kellie Matthews, a resident who was lead author of the study.

Overall, the women's risk of HNPCC was three times higher than expected, added Dr. Rodney Rocconi, a fellow in gynecologic oncology.

For women who were not obese, it was six times as high. Consequently, the investigators urged that special attention be paid to those with a body mass index less than 30, even though they recommend that all endometrial cancer patients younger than age 50 be screened for HNPCC.

The Roswell Park group looked for HNPCC mutations in 77 patients in the Gilda Radner Familial Ovarian Cancer Registry. None had tested positive for BRCA gene mutations, and none met the Amsterdam criteria for diagnosing HNPCC.

The investigators reported that two patients tested positive for mutations in the MSH2 gene, and eight others had suspicious base-pair substitutions in the MLH1 or MSH2 genes.

Had the Amsterdam criteria included a family history of ovarian cancer, 13 patients would have been recognized as being at high risk for HNPCC.

Risk-reducing surgery at age 30 is the most cost-effective option long term, though initially, it's the most expensive.

DR. CHEN

"HNPCC should be considered in families with familial ovarian cancer if BRCA has been ruled out," said Dr. Kerry Rodabaugh, senior author.

"We only identified 2 out of 77 patients with familial ovarian cancer to have HNPCC, but these 2 were previously unidentified and are probably unaware of their risk for colon cancer," she added.

Dr. Rodabaugh said that she hoped the findings would lead to greater awareness of the relationship of gynecologic cancers to HNPCC.

Women who have HNPCC are known to be at risk of developing ovarian cancer, she said; it is recognized as a component of the syndrome, but not as a diagnostic criterion.

For women who have HNPCC, dealing with the risk of gynecologic cancer can be a lifelong endeavor with serious effects on quality of life, according to Dr. Chen. The primary options are:

► Risk-reducing surgery;

► An annual screening with ultrasound, CA-125 test, endometrial biopsy, and a medical examination; or

► An annual examination without special screening.

Dr. Chen and her associates applied a statistical model to data on cancer mortality and costs and found that risk-reducing surgery at age 30 was the most cost-effective option.

It is the most expensive option initially, but becomes less costly over time, according to Dr. Chen. By preventing cancer, the costs of annual screenings and examinations and of treating gynecologic cancers are eliminated.

Although the study's primary end point was cost-effectiveness, the calculations included survival.

Life expectancy was longest (80 years) among patients who had risk-reducing surgery, compared with 79 years in those who had annual screening, and 77 years in those who had only an annual examination. ■

DRUGS, PREGNANCY, AND LACTATION

Prenatal Use of SSRIs

Studies released over the last year have raised a spectrum of concerns regarding the use of antidepressants during pregnancy, whereas others have brought into focus the risk for new onset or relapse of depression during pregnancy and the impact of maternal depression during pregnancy on obstetrical outcome and neonatal well-being. These findings received a considerable amount of attention in the literature and in the media.

Among the concerns raised was the extent to which fetal exposure to one selective serotonin reuptake inhibitor (SSRI)—paroxetine—has been associated with an increased risk for cardiovascular malformations. In other studies, SSRI use during pregnancy was associated with compromised neonatal adaptation with symptoms of jitteriness, tachypnea, and tremulousness, which is known as "neonatal abstinence syndrome."

BY LEE COHEN, M.D.

This finding of transient neonatal jitteriness and tremulousness has been highly consistent across studies dating back to the mid-1970s, when similar concerns were raised with prenatal exposure to the older tricyclics. About 25% of children who are born to mothers treated with SSRIs, particularly late in pregnancy, appear to have these symptoms.

It is noteworthy, however, that the clinical relevance of the syndrome seems small. Even in the most rigorous study to date, which described a subgroup of children exposed in utero to SSRIs, those who had these symptoms required no particular treatment interventions during the acute neonatal period. (OB. GYN. NEWS, April 15, 2006, p. 12).

Also reported last year was our collaborative study with investigators at the University of California, Los Angeles, and Emory University, Atlanta, demonstrating that the rate of depressive relapse associated with antidepressant discontinuation during pregnancy is high—about 70%—compared with 25% among pregnant women who maintained treatment with these medicines across pregnancy.

These new data on teratogenicity, treatment-emergent neonatal syndromes, and relapse risk have provided more well-delineated information on the risks and benefits of antidepressant use during pregnancy.

The information is extremely important in this setting, because antidepressant use during pregnancy in the United States may be as high as 4%-6%, based on estimates by some of our recent work.

A study published last summer by investigators from the University of Michigan, Ann Arbor, illustrates the fact that while depression is relatively common during pregnancy, most women at risk for illness don't receive any treatment, and, when treatment is prescribed, it is often suboptimal.

In the study, 1,837 pregnant women from five hospital-affiliated obstetrics clinics were screened for depression, 276 of whom were identified as being at risk. Only 20% of the at-risk women were receiving some form of antidepressant treatment. Of the group getting treatment, 48% received a combination of medication and counseling with psychotherapy, 21% received antidepressants only, and 31% received psychotherapy only. Still, in many cases, treatment was inadequate. Only 43% of those taking antidepressants for 6-8 weeks were given the recommended daily dose.

Among the women who met the criteria for major depressive disorder, only 33% received any type of treatment; only 11% received what was reported to be adequate antidepressant therapy (Gen. Hosp. Psychiatry 2006;28:289-95). The low rate of treatment of depression during pregnancy may reflect concerns regarding the effects of antidepressants on the fetus. However, even women in the study who received psychotherapy alone did not receive an adequate intensity of treatment.

One has to wonder whether these findings reflect concerns over the past year about fetal exposure to antidepressants. It is notable that, even when a clinical decision is made to use antidepressant therapy, treatment is incomplete.

Incomplete treatment of depression during pregnancy represents a failure in clinical risk-benefit decision, because the woman and child are exposed to both medication and the adverse effects of the disorder. And clinical depression that is untreated during pregnancy is the strongest predictor of postpartum depression—which can have enduring effects for the patient, her newborn, and her family.

The Michigan study underscores the need for effective strategies to detect and treat women at risk for depression during pregnancy. Sustaining euthymia and maintaining emotional well-being during this period should be our major clinical goals.

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