Ovarian Cancer Blood Test Accuracy Rates Improved

BY JANE SALODOF MACNEIL
Southwest Bureau

SAN DIEGO — Refinements to an experimental blood test for ovarian cancer have made it 97.5% sensitive and 99.7% specific for this rare, hard-to-detect disease, Dr. Aliza L. Leiser reported at the annual meeting of the Society of Gynecologic Oncologists.

"This test can discriminate between disease-free women and early cancer patients," Dr. Leiser said in a presentation of validation studies conducted with serum samples from 160 newly diagnosed ovarian cancer patients and 365 healthy controls.

The investigators have started a prospective longitudinal trial to evaluate the screening tool in high-risk patients. Dr. Leiser, of Yale University, New Haven, Conn., said the group hopes to enroll 250-300 women. Participants are to submit blood samples every 3 months and undergo frequent transvaginal ultrasound and CA-125 screening.

Two years ago, Dr. Gil Mor of Yale's department of obstetrics, gynecology, and reproductive medicine announced that he and his colleagues had achieved 95% specificity, 95% sensitivity, 95% positive predictive value, and 94% negative predictive value with a four-protein blood test (Proc. Natl. Acad. Sci. U.S.A. 2005 May [Epub doi:10.1073/pnas.0502178102]). The test was considered highly promising, but the investigators said it had to be made at least 99.6% specific to avoid a high false-positive rate in the general population.

The revised test adds two more proteins—macrophage inhibitory factor and CA-125—to the original four-protein set of leptin, prolactin, osteopontin, and insulinlike growth factor II. Using bead-based multiplex technology, it determines levels of all six biomarkers simultaneously from a single blood sample. The new test also had a positive predictive value of 99.3% and a negative predictive value of 99.2% in the validation studies. It misclassified four stage I-II cancers; all stage III-IV cancers were identified correctly.

Applying these results to a 1 in 2,500 incidence of ovarian cancer in the general population, Dr. Leiser said its positive predictive value would be 12.6% and its negative predictive value 99.2%. She said the test is 91% sensitive for stage I-II disease and 100% sensitive for stage III-IV disease.

In a discussion of the study, Dr. Laura J. Havrilesky, of Duke University, Durham, N.C., noted, however, that only 24% of ovarian cancers in the validation studies were stage I-II cancers. "The test is useful only if it results in reduction of disease-related mortality, and this would be best achieved if it results in detection of the early-stage cancers."

Dr. Leiser said that finding a sufficient number of early-stage patients is difficult because the disease is rarely detected when it is most treatable. She said her group is soliciting samples from other centers to expand the validation studies to a larger pool of patients with early-stage disease. The group also is trying the test in 1,200 healthy controls and 500 patients with other cancers and inflammatory conditions that might affect expression of the same biomarkers. The results so far have been negative in all patients with endometrial cancer, she said.

For information on submitting blood samples for testing, visit www.yaleobgyn.org/oncology/ovarian_cancer.html. ■

Cisplatin May Be Effective Option for Patients Who React to Carboplatin

HOT SPRINGS, VA. — Patients with ovarian cancer who have a hypersensitivity reaction to carboplatin can be successfully treated with cisplatin without a lengthy desensitization procedure, Dr. Megan Callahan said at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists.

She presented a review of 24 women with ovarian cancer who received cisplatin after an allergic reaction to carboplatin. It is the largest case series to date.

Carboplatin hypersensitivity is correlated with the number of treatment cycles experienced, said Dr. Callahan of the University of Virginia, Charlottesville. "The cumulative risk increases from 0.92% for less than five cycles to 6.5% for six cycles, and up to 19% for eight cycles," she said. Her patients' reactions occurred at a median of 10 cycles. None of the reactions was life threatening.

All of the patients were rechallenged with cisplatin in a subsequent treatment cycle. The drug was given at a standard infusion rate over 1.5 hours. None of the patients received desensitization with steroids or antihistamines.

Most (18) were able to tolerate the full number of cisplatin treatment cycles without a hypersensitivity reaction. Only one of the six who reacted to cisplatin did so in the first cycle. The rest were able to tolerate 1-6 cycles before having a reaction. All of the cisplatin reactions were managed conservatively on an outpatient basis.

Dr. Callahan's 24 patients bring the total reported in the literature to 57. Among these patients, only seven had cisplatin reactions, and one died. "This results in an 86% success rate for cisplatin rechallenge."

She added that she has not been able to identify any predisposing factors that might predict which patients would react to either drug. "We looked at past medical history, reported allergies, and concurrent medications, and we couldn't identify anything." The severity of the initial carboplatin reaction also did not help predict which patients would later experience a cisplatin reaction.

—Michele G. Sullivan

DRUGS, PREGNANCY, AND LACTATION

Cocaine Use by Pregnant Women

Concerns about the adverse effects of maternal cocaine use during pregnancy on children exposed in utero have been the focus of many studies since the 1980s, when cocaine use began to increase, first among more affluent socioeconomic groups, then among lower income groups with the advent of cheap crack cocaine.

During the mid to late 1980s, reports suggested cocaine use during pregnancy caused congenital malformations, and later reports suggested such use had adverse effects on long-term neurodevelopment in children. But more recent systematic reviews of a large number of cases have not found an association between in utero exposure to cocaine and an increase in malformations of any kind, and these original concerns have not been borne out.

BY GIDEON KOREN, M.D.

Women who use cocaine have many other risk factors for poor neonatal outcome and adverse long-term effects on the child than do women who don't use cocaine, such as low socioeconomic class, smoking, poor nutrition, and abuse of other drugs.

Over the years, studies have more carefully controlled for these other factors, comparing women who used cocaine during pregnancy to women in similar environments, who had the same risk factors but did not use cocaine, and these studies have not found any association between maternal cocaine use and congenital defects or long-term effects in children.

In 2001, investigators performing a review of 36 prospective studies of prenatal cocaine exposure in children aged 6 years and younger found no convincing consistent evidence that in utero cocaine exposure was associated with negative effects on physical growth, developmental test scores, or receptive or expressive language (JAMA 2001;285:1613-25).

Although these and later studies constitute the overall picture, data from some studies have suggested that prenatal cocaine exposure does have some serious adverse effects, most notably, a greater risk of prematurity and higher rates of placenta previa.

There are also reports that some addicted women take high doses of cocaine near the end of pregnancy because they believe it may induce labor, which can result in placental bleeding and shock, potentially resulting in adverse, long-term effects on brain development in the baby.

An important consideration for obstetricians and other health care professionals who follow women who may use cocaine during pregnancy and those who follow their children is that continuing use of cocaine after a woman knows she is pregnant is recognized as essentially a sine qua non for addiction.

Many women may not disclose they use cocaine during a history, but our laboratory and others have developed methods of ascertaining whether a baby has been exposed to cocaine in utero, such as analysis of neonatal hair and meconium, which are biomarkers for maternal cocaine use that are validated and widely used by social services and clinicians in the United States and Canada.

Cocaine and its metabolite benzoylecgonine accumulate in fetal hair during the last trimester, so a positive test is a strong indicator the mother used cocaine during the sixth or seventh months. They also accumulate in meconium, produced in midpregnancy, so a positive meconium test indicates use during pregnancy. A meconium analysis can be used in the first few days post partum; the hair analysis can be used up to 3 months postpartum.

Studies have documented damage to the brain in monkeys exposed in utero to cocaine at doses equivalent to doses that are typically used in humans. Why similar findings have not been found in human studies speaks volumes to the plasticity of the newborn's or young child's brain and the ability to recover, if early environmental factors, with optimal stimulation, are favorable. This is an important area of research that is not yet fully resolved.

We conducted a study comparing children exposed in utero to cocaine who had been adopted by stable families, where presumably, environmental factors were normal, to biologic children of mothers from the same socioeconomic class.

The IQs of the adopted children were significantly lower than the comparator group, although the families were not aware of any neurodevelopmental problems with the children. This suggests that even in an optimal situation, however, not all damage could be reversed by brain plasticity.

We and others continue to follow children exposed in utero to cocaine and are trying to understand sources of variability and why some children are affected and others are not.

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