Urine Test Enhances Breast Ca Risk Picture

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — A simple urine test for selected matrix metalloproteinases may provide a novel noninvasive means of assessing a woman's risk of developing breast cancer, Dr. Susan E. Pories reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Urinary levels of two biomarkers—matrix metalloproteinase-9 (MMP-9) and a disintegrin and metalloprotease 12 (ADAM12)—appear to be independent predictors of the presence of breast atypical hyperplasia or lobular carcinoma in situ (LCIS), both of which are well established predictors of increased risk of breast cancer, explained Dr. Pories of Beth Israel Deaconess Medical Center, Boston.

She and her coworkers had previously found that levels of MMP-9 and ADAM12 increase with more advanced disease status in breast cancer patients.

In the current study, Dr. Pories reported on urine samples obtained from 44 women with atypical ductal or atypical lobular hyperplasia, 24 with lobular carcinoma in situ, and 80 healthy controls.

For a 30-µL urine sample testing positive for both MMP-9 and ADAM12, the probability that the sample belonged to a woman with LCIS or atypical hyperplasia was 100%.

A urine sample that was MMP-9 negative but ADAM12 positive had a 67% probability of being associated with atypical hyperplasia and a 50% likelihood that the patient had LCIS.

An MMP-9-positive/ADAM12-negative urine sample conferred a 40% chance that the patient had LCIS and a 25% chance that she had atypical ductal hyperplasia or atypical lobular hyperplasia.

And a sample that proved negative for both biomarkers was associated with a zero probability of atypical hyperplasia.

The urine test has the advantages of being less invasive, costly, and uncomfortable than mammography.

Asked how she envisions the urine test being used, Dr. Pories said in an interview that although it will never replace mammography, it could end up as a useful adjunct, serving, for example, as a tie breaker in helping to decide whether to biopsy a woman with a Breast Imaging Reporting and Data System (BI-RADS) stage 3 or 4 mammogram.

In high-risk women, the test could also be performed between scheduled mammograms in order to provide early warning of a change in status even before a mass appears.

Dr. Pories added that further studies with larger numbers of patients are needed to ensure the validity of the urine test. The investigators are looking for a commercial partner to develop their assay. ■

Many At-Risk Women Opt for Lifestyle Changes Over Tamoxifen

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Lifestyle approaches to breast cancer risk reduction have assumed considerable importance for the many women who have turned a cold shoulder to tamoxifen for chemoprevention, according to Leslie Bernstein, Ph.D., professor of preventive medicine at the University of California, Los Angeles.

"In my discussions with colleagues, word of mouth is that women are not flocking to take tamoxifen to reduce their high risk of breast cancer," she observed at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This anecdotal impression is borne out by the recent literature. In three of four studies of tamoxifen's acceptance for prevention of breast cancer by high-risk women after counseling about the extent of their risk and the pluses and minuses of tamoxifen, only 3%-15% of candidates opted for therapy, although in another study the rate was 42%.

A recent report by Debora A. Paterniti, Ph.D., and coworkers at the University of California, Davis, Center for Health Services Research in Primary Care provides insight into why so many eligible women are unwilling to take tamoxifen for chemoprevention.

In focus groups involving ethnically diverse populations of women at substantially increased risk for breast cancer, the investigators found that participants were actually less inclined to take tamoxifen after receiving a standardized educational intervention.

They were leery of taking a drug for 5 years to protect against a disease they might not develop. They were also quite concerned about tamoxifen's potentially serious side effects. And they were uneasy about the reliability of scientific studies (Ethn. Dis. 2005;15:365-72).

"It doesn't make you very heartened about the research we do, since we seem to have great confidence in what we're doing," Dr. Bernstein commented.

The women felt they had nonpharmacologic options to reduce their breast cancer risk. They cited early detection, faith, diet, and complementary and alternative therapies.

"When I see the other options they list, it makes me realize that we have a long way to go to educate women about what other options might actually be available to them," Dr. Bernstein said. ■

DRUGS, PREGNANCY, AND LACTATION

The FDA Advisory on Paroxetine

Multiple studies over the past decade have been supportive of the reproductive safety of the selective serotonin reuptake inhibitors (SSRIs) when used during the first trimester; these studies include one recent metaanalysis and other extensive reviews. Particularly reassuring have been the prospective data on fluoxetine (Prozac) and citalopram (Celexa). As a result, clinicians have been relatively reassured about the absence of teratogenic risk associated with the SSRIs.

BY LEE COHEN, M.D.

New concerns were recently raised about the reproductive safety of paroxetine by a presentation at the Teratology Society annual meeting that reported an increased risk of omphalocele associated with first-trimester exposure. This report was based on preliminary, unpublished data from the National Birth Defects Center, which I reviewed in a recent column (FAMILY PRACTICE NEWS, Nov. 1, 2005, page 41). A weaker association was also found between omphalocele and other SSRIs.

A Food and Drug Administration public health advisory about paroxetine followed in December, describing preliminary results of two other unpublished studies indicating that paroxetine exposure in the first trimester may increase the risk of congenital malformations, particularly cardiac malformations. At the FDA's request, paroxetine manufacturer GlaxoSmithKline has changed the pregnancy category label for paroxetine from C to D.

It is surprising that the FDA's recommendation and advisory are based on preliminary analyses from several recent, unpublished, non–peer-reviewed epidemiologic studies, as these are data that should be considered, at least at this point, inconclusive.

Using data from the Swedish National Registry, one study found a 2% rate of cardiac defects among infants exposed during the first trimester to paroxetine vs. 1% among all registry infants. But a previous study using registry data that was based on a slightly smaller number of children exposed to paroxetine did not report this association (J. Clin. Psychopharmacol. 2005;25:59-73).

Another study, using data from a U.S. insurance claims database, found the rate of cardiovascular malformations was 1.5% among infants exposed to paroxetine during the first trimester vs. 1% among infants exposed to other antidepressants. The majority were atrial or ventricular septal defects, which are common congenital malformations.

The modest increases in relative risk of a common anomaly, when derived from a claims database with inherent methodologic limitations, make interpretation of these data problematic. Unfortunately, the language in the FDA advisory, suggesting that "the benefits of continuing paroxetine may outweigh the potential risk to the fetus," may get lost in the information patients receive.

Although there are not as many published studies on the teratogenic risk of paroxetine as for other SSRIs, it is noteworthy that prospective studies have not identified a higher rate of congenital or cardiac malformations associated with prenatal exposure to paroxetine.

How does the clinician then counsel women of reproductive age who suffer from major depression? And what is the best option for patients who are being treated with paroxetine who want to get pregnant or who have an unplanned pregnancy? Until the issue is clarified with more rigorously obtained and conclusive data, it is reasonable to avoid paroxetine in these women.

For those with major depression who are antidepressant-naive, it may be most prudent to prescribe an SSRI or an SNRI for which there are no unfavorable data to date, such as fluoxetine or citalopram/escitalopram, or an older tricyclic antidepressant such as nortriptyline.

What makes sense for those who have failed to respond to one of those medications previously, as in the all-too-common scenario of nonresponse to multiple SSRIs and response only to paroxetine? In this situation, the use of paroxetine in women who are planning to conceive or who are already pregnant should not be considered absolutely contraindicated.

If the medication is discontinued before or during pregnancy, it should be done gradually, as is consistent with standard clinical practice.

Until the data are peer-reviewed and published, decisions about use of this medicine in women who are planning a pregnancy or are pregnant will have to be made on a case-by-case basis. But we need to keep in mind that nothing is more critical than sustaining euthymia during pregnancy. Untreated depression in pregnancy is associated with compromised fetal well-being as well as increased risk for postpartum depression.

The FDA advisory is available online at www.fda.gov/cder/drug/advisory/paroxetine200512.htm.

DR. COHEN *directs the Perinatal and Reproductive Psychiatry Program at Massachusetts General Hospital, Boston, which offers information about pregnancy and women's mental health at www.womensmentalhealth.org. He is a consultant to manufacturers of several antidepressant drugs, including paroxetine and other SSRIs.*