Offer FMR1 Testing in 46,XX Early Ovarian Failure

BY MARY ELLEN SCHNEIDER
New York Bureau

TORONTO — Women with spontaneous 46,XX premature ovarian failure are at increased risk of having a premutation of the fragile X mental retardation 1 gene and should be informed of the availability of testing for fragile X, Dr. Lawrence M. Nelson said at the annual meeting of the Endocrine Society.

But appropriate counseling must be provided before the test is administered, said Dr. Nelson, head of the integrative reproductive medicine unit at the National Institute of Child Health and Human Development, part of the National Institutes of Health. Dr. Nelson is also a commissioned officer in the U.S. Public Health Service.

These findings are part of a draft statement being developed by scientists, clinicians, and patient advocates with input from others around the world. The American Society for Reproductive Medicine and the National Institutes of Health convened experts last October to work on draft guidelines for the identification and management of the FMR1 premutation and premature ovarian failure. The draft is available online at www.fmr1pof.com, and comments can be submitted at the Web site.

'It's a dual threat to the parental role because it's a cause of infertility and it's a genetic risk factor.'

DR. NELSON

Premutations of the FMR1 gene have been associated with a spectrum of reproductive issues, including infertility, poor response to gonadotropin stimulation, menstrual irregularity, and symptoms of estrogen deficiency. The presence of the FMR1 gene can also indicate genetic disorders within a family, including fragile X syndrome, which can cause mental impairment, autism, or neurodegenerative disorders. About 6% of women with spontaneous 46,XX premature ovarian failure have the FMR1 premutation, Dr. Nelson said.

"It's a dual threat to the parental role because it's a cause of infertility and it's a genetic risk factor for having a child with mental retardation," Dr. Nelson said. "So we need to handle genetic testing with great sensitivity."

In the draft document, experts recommended that physicians obtain an accurate and detailed family history to detect the presence of fragile X–associated disorders in all women presenting for reproductive care. The Office of the Surgeon General has developed an online tool called "My Family Health Portrait" that patients can use to enter their family medical history and then print it out for their physician, Dr. Nelson said. The tool is available online at http://familyhistory.hhs.gov.

FMR1 testing should be offered to women who are diagnosed with premature ovarian failure. In addition, physicians should consider FMR1 testing in women with reproductive or fertility problems associated with elevated basal FSH levels and those with low response to gonadotropin stimulation, according to the draft.

But physicians should undertake testing only after the patient has been informed that a positive test result has implications beyond their own health and that other family members could be at risk for associated conditions.

Patients should also have the option not to undergo FMR1 testing. Although finding an FMR1 premutation could help explain the cause of premature ovarian failure, it does not rule out other causes, Dr. Nelson said.

FMR1 test results should include a list of the number of CGG repeats, and written interpretations should be stratified as normal, intermediate, premutation, or full mutation, according to the draft document. The molecular analysis should include obtaining the CGG repeat number through both polymerase chain reaction assay and Southern blot assay. In addition, the lab should check the FMR1 gene methylation status. The total cost of the tests is generally about $300, Dr. Nelson said.

Any results that do not come back as normal should be discussed with patients face to face, the group recommended. "This is not an average lab test where you can call and give the patient the results over the telephone," Dr. Nelson said. ■