Ovarian Aging May Be Missed as Infertility Cause

By Alicia Ault
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A S H V E I L L E , N. C. — Ovarian aging is often overlooked as a cause of infertility and should be considered in younger women, Dr. Tamer M. Yalcinkaya said at the Southern Obsteric and Gynecological Society meeting.

Dr. Yalcinkaya, medical director of the in vitro fertilization program at Wake Forest University, Winston Salem, N.C., said that ovarian aging is an evolving concept. It encompasses age-related infertility, diminished ovary reserve, and early menopause. Ovarian aging often is hidden among the “unexplained” causes of infertility, but it is as common as many of the factors usually examined and is more severe and less treatable, said Dr. Yalcinkaya.

Ovarian aging is linked to increased pro- gressive follicular depletion and/or abnormal- ities in the oocyte/ follicle. Oocytes are continually declining from birth to menopause, but the decrease accelerates starting at age 38, he said, citing a 2005 study (Engl. J. Med. 2005;353:64-73). At the same time, there is an increase in basal follicle-stimulating hormone (FSH) levels, a decrease in fecundity, and an increase in aneuploidy. While endocrine and men- strual functions remain relatively un- affected, Yalcinkaya said that pro- gressive changes in the ovaries result in irregularities generally begin at 45. By menopause, there are 1,000 or fewer follicles. The mean age of menopause is 51, though it ranges from 40 to 60. The age of onset is primarily determined by ge- netic factors but is slightly influenced by lifestyle, environmental, and parity factors.

Ten percent of the population will have early menopause—that is, by age 45—and another 10% will show early ovarian aging, when they are aged 27-32, said Dr. Yalcinkaya. Women of reproductive age can experience ovar- ian aging, he said. However, women with diminished ovarian reserve still have the potential to conceive, and it is important to identify these women early so that var- ious assisted reproductive techniques can be attempted, Dr. Yalcinkaya.

Diagnoses include baseline hormone measurements, including early follicular phase FSH, estradiol, inhibin B, and antimuller- ian hormone. Ultrasound can be used to count the number of antral follicles if the technician can exclude the possibility of mea- sure ovum volume. A threshold of 3 cm is used to predict poor outcome with in vitro fertilization, he said. FSH levels were shown to the adverse events causing discontinuation in a study published in Fertility and Sterility (2003;79:1091-10). Dr. Yalcinkaya said. Normal is less than ten IU/L. Measures of 10-15 indicate a minimal decrease in ovarian re- serve; 15-20, severely diminished; and greater than 20, the pregnancy chances are almost zero, he said.

Horizons should be challenged with clomiphene citrate, exogenous FSH reserve, and gonadotropin-releasing hor- mone agonist stimulation. The clomiphene citrate challenge may be better at detecting diminished ovarian reserve than the FSH test but can only be used in patients over age 35, he said. Of- ten, patients who have an abnormal clomiphene citrate test are told they have “ovulatory disorder” or “unexplained in- fertility,” but clinicians should investigate further to as the cause of ovarian aging is present.

The clomiphene citrate test may be performed to evaluate ovarian reserve. To identify the women early and include various factors that may affect the outcome of a follicle, he said. Measurements, including baseline hormone measurements, including early follicular phase FSH, estradiol, inhibin B, and antimullerian hormone. Ultrasound can be used to count the number of antral follicles if the technician can exclude the possibility of measuring ovum volume. A threshold of 3 cm is used to predict poor outcome with in vitro fertilization, he said. FSH levels were shown to be elevated in a study published in Fertility and Sterility (2003;79:1091-10). Dr. Yalcinkaya said. Normal is less than ten IU/L. Measures of 10-15 indicate a minimal decrease in ovarian reserve; 15-20, severely diminished; and greater than 20, the pregnancy chances are almost zero, he said.

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The clomiphene citrate challenge may be better at detecting diminished ovarian reserve than the FSH test but can only be used in patients over age 35, he said. Often, patients who have an abnormal clomiphene citrate test are told they have “ovulatory disorder” or “unexplained in- fertility,” but clinicians should investigate further to as the cause of ovarian aging is present. Dr. Yalcinkaya said. The inhibin B test is new and evolving, with divergent data on its utility, he said.

Most of these tests have a low positive predictive value; good results mean the clinician can’t guarantee that the patient will become pregnant. But they also have a high negative predictive value; abnormal results generally mean a pregnancy is highly unlikely, Dr. Yalcinkaya.

Ovarian aging can’t be stopped, but physicians can counsel women to main- tain healthy lifestyles that promote ferti- lity, including quitting smoking. Physi- cians can also consider liberal testing of ovarian reserve in all infertile women who are over age 35 or who have a single ovary, in women with a history of ovar- ian surgery; and in women who smoke or have unexplained infertility, recurrent un- explained early pregnancy losses, irre- gular periods, or a family history of early menopause, he said. It is important to moderate ovarian aging should be referred to a reproductive endocrinologist for ag- gressive treatment with exogenous go- nadotropin-releasing hormone agonist or in vitro fertilization, he said. Dr. Yalcinkaya had no conflicts of in- terest to disclose.