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Endometrial Biomarkers Can Improve Success of Fertility Therapy

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By Karla Gale

NEW YORK (Reuters Health) Jul 21 - A new endometrial function test (EFT) provides information that can often lead to improved outcomes of assisted reproduction modalities, according to a research team at Yale University School of Medicine.

The EFT uses immunohistochemical staining to evaluate cyclin E and p27 levels in formalin-fixed, paraffin-embedded biopsy samples of the developing endometrium, Dr. Harvey J. Kliman and colleagues report in the July issue of *Fertility and Sterility*.

The research team, based in New Haven, Connecticut, examined more than a dozen different markers and found that cyclin E and p27 "stained cleanly and specifically, and go through the most significant changes during the menstrual cycle," Dr. Kliman told Reuters Health. Cyclin E is the rate-limiting activator of the mitotic G1 to S phase transition, he explained, and the cyclin-dependent kinase inhibitor p27 inhibits cyclin E to prevent cell cycle progression.

The researchers report their findings for 48 biopsy samples from 23 volunteers with no history of infertility, 130 from 83 naturally cycling women seeking treatment for infertility, and 40 samples from 23 infertile women who had undergone mock cycles in preparation for oocyte donation.

In normal endometrium, they observed cyclin E only in the estrogen-controlled proliferative phase and the early secretory phase, Dr. Kliman said. Glandular cyclin E progressed from the cytoplasm into the nucleus, so that nuclear staining was maximal at day 19. By days 23 to 27, no more than trace staining was observed in either the cytoplasm or the nucleus.

In nonfertile women, 60% of biopsy samples revealed persistent cyclin E staining, indicating cells that are developmentally delayed and arrested at an earlier stage of the menstrual cycle. Using a cutoff of 10%, cyclin E nuclear staining in biopsy samples dated as cycle day 21 or greater were significantly different in fertile and infertile ($p = 0.00000065$) women, with a sensitivity of 60% and a specificity of 95%.

The mock cycle group also differed significantly in cyclin E staining ($p = 0.02$). The sensitivity was 38% in differentiating these women from normal fertile women, and specificity was 95%.

The EFT is valuable for women who have failed previous in vitro fertilization cycles, Dr. Kliman said. After identifying

an abnormal EFT, patients' stimulation protocols can be modified so that oocytes can be successfully implanted.

The EFT also provides insight into the biochemical and developmental state of endometrial glands, Dr. Kliman added. It represents "a good overall test of the functional state of the organ," and thus a research tool for understanding other clinical conditions of pre- and postmenopausal women.

The group has submitted international patent applications. Clinicians can submit endometrial biopsy samples for EFT analysis using a protocol described at <http://info.med.yale.edu/obgyn/kliman/Infertility/DX/diagwelcome.html>.

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