

Reply

To the Editors:

I appreciate the comments by Drs. Nelson and Merriam concerning our manuscript. Space did not allow us to mention all the possible hypothetical explanations of the mechanisms by which ovulation and pregnancy can occur in an apparent menopausal woman. We used, as an example, the down-regulation of gonadotropin receptors hypothesis because this was the model on which we based our therapy. However, frequently in medicine a therapy may be found effective although the initial premise on which that therapy was based is wrong.

The alternate explanation of autoimmune oophoritis suggested by Drs. Nelson and Merriam is certainly plausible and could well explain the events in this case. Perhaps the presence of a preexisting cyst might favor an autoimmune oophoritis rather than a gonadotropin receptor down-regulation mechanism. Unfortunately, although we did obtain a fasting glucose, calcium level, thyroid studies including thyroid-stimulating hormone, cortisol, complete blood cell count, and serum cortisil (all of which were normal), we did not measure specific antibody levels against any of the endocrine glands. While the majority of cases of autoimmune oophoritis have been associated with Addison's disease,^{1,2} there also have been cases reported with documented autoimmune ovarian histopathology without adrenal disease.³

As of now, there have been 21 pregnancies in the first 100 apparent ovarian failure cases that we treated with gonadotropin suppression and subsequently with human menopausal gonadotropin stimulation (10 have been delivered of normal viable babies) and in only one case was there documentation of paucity of ovarian tissue.⁴ We had an additional case in which there was hardly any ovarian tissue remaining in a 44-year-old woman with bilateral blocked tubes. In that case we fertilized an embryo by in vitro fertilization but it was cryopreserved rather than transferred for future use because donor sperm was also required.⁵ These two cases both favor the gonadotropin receptor down-regulation mechanism hypothesis. However, we have no further histologic or morphologic description of the ovaries of any of the other cases, so that either an autoimmune oophoritis or gonadotropin receptor down-regulation mechanism for "ovarian failure" could be the cause. In fact, other mechanisms are also possible (e.g. spontaneous remission from gonadotropin receptor antibodies) as we have previously suggested.⁴

We are very interested in the results of Drs. Nelson and Merriam's clinical trial of a long-acting gonadotropin releasing hormone analog for women with ovarian failure. It is certainly possible that our occasional success with ovulation induction with leuprolide acetate alone occurred not on the basis of restoring gonadotropin receptors to such a degree that the patient responded to a combination of endogenous gonadotropin and the agonistic action of leuprolide, but, instead by

providing an "ovarian respite." However, in the case we reported the rapid response to leuprolide before there was time to suppress or rest the follicle does indeed favor the gonadotropin receptor down-regulation mechanism rather than the autoimmune oophoritis hypothesis.⁶

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