

Ovarian Failure and G-Proteins—Do We Really Need to Know How They Work?

To the Editor:

I read with interest the Nelson et al. study (1) concerning failure to determine any increase in ovulation rate in women using the gonadotropin-releasing hormone agonist (GnRH-a) deslorelin compared with placebo controls.

The authors' hypothesis centered on belief that the majority of patients with premature ovarian failure have a type of autoimmune folliculitis and that resting the ovary from a trigger antigen might allow completion of follicle maturation. If their selection of cases truly did not have autoimmune follicular destruction (probably did not, considering absence of antiovarian antibodies, adrenal insufficiency, and rare low "positive" autoimmune tests), it is not surprising that no additional benefit of GnRH-a therapy could be determined. We believe the most common cause is actual atresia of follicles and have even published a case of ovulation and pregnancy after estrogen and human menopausal gonadotropin (hMG) treatment in a woman with streaked ovaries (2).

Nelson et al. allude to our previous publication of 100 cases of uncontrolled treatment of ovarian failure (I believe we are the unusual asterisk in the references) (3). However, although they employed controls, their methodology does not really answer some key questions concerning treatment and response of this condition. Does estrogen increase gonadotropin receptor sensitivity or is spontaneous ovulation just as likely to occur? (Unfortunately, a control group without estrogen therapy was not included.) Is the mere replacement of estrogen the critical therapeutic factor or will reduction of elevated gonadotropins to a certain critical level (whether by estrogen or GnRH-a) allow restoration of down-regulated gonadotropin receptors? We favor the latter theory because we have observed ovulation after a short course of leuprolide therapy in hypergonadotropic females (3-5).

The authors explain why, based on their hypothesis, they did not utilize hMG. However, because their hypothesis was not substantiated, their recommendation to not use hMG has no basis. We have subsequently modified therapy for cost efficiency, i.e., use of hMG only, when a follicle has been re-

cruted by estrogen therapy as evidenced by a rise in estradiol (E_2) (ethinyl/ E_2 used very little cross-reactivity) (3). Randomized studies needed are estrogen versus placebo in recruiting follicles and hMG versus placebo in completing maturation of the follicle.

Even without proof of mechanism for follicular recruitment, the authors' data confirm that ovulation can occur despite elevated gonadotropins. Careful observation can enable better timing of intercourse, possible introduction of human chorionic gonadotropin if nonrelease is demonstrated by sonography, and luteal phase support if needed. These therapeutic measures may improve pregnancy rates in women with this condition.

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Reply of the Author:

The pathophysiologic mechanism for premature ovarian failure remains unidentified in most patients. This leads to empirical therapy. Our con-

trolled study evaluated gonadotropin suppression therapy in patients with karyotypically normal spontaneous premature ovarian failure and found no benefit. We did not claim to be treating a pure group of patients with autoimmune ovarian failure, and we specifically addressed this point in our article (1).

Dr. Check believes the most common cause of premature ovarian failure is follicular atresia related to down-regulated gonadotropin receptors, but this has never been demonstrated in the follicles of patients with premature ovarian failure. In contrast, autoimmune ovarian failure is a well-documented histologic entity, and, as a group, patients with chromosomally competent premature ovarian failure have increased peripheral T-lymphocyte activation (2, 3). There is no practical clinical method of known positive and negative predictive value to identify autoimmune ovarian failure. Therefore, patients may present for therapy with unrecognized autoimmune premature ovarian failure.

Dr. Check states that we have no basis on which to recommend against human menopausal gonadotropin (hMG) therapy in patients with hypergonadotropic amenorrhea. We found an ovulation rate of 17% during observation of these patients (1). Dr. Check refers to his uncontrolled series of 100 consecutive women with hypergonadotropic amenorrhea, in whom he claims a 19% ovulation rate during hMG therapy (4). His claim to a 19% ovulation rate may be artificially high due to selection bias. In reality, Dr. Check reported on 100 consecutive patients with hypergonadotropic amenorrhea "who allowed at least four treatment cycles (4)." Undoubtedly, patients who may have ovulated by chance during the first few treatment cycles were encouraged and would have been more likely to continue this expensive therapy than patients who remained anovulatory during the first few cycles. If Dr. Check had included his patients who stopped treatment after completing one to three treatment cycles, his ovulation rate with hMG therapy would likely have been much less than 19%.

Other autoimmune endocrine disorders are exacerbated by trophic stimulation of the affected gland (5), possibly by increasing antigenic load. The same may be true for patients with unrecognized autoimmune ovarian failure. With controls and unbiased patient selection, Dr. Check might even have demonstrated that hMG therapy reduces the ovulation rate in patients with hypergonadotropic amenorrhea (4). Effectiveness for hMG therapy in premature ovarian failure has not been demon-

strated, and there is a theoretic possibility that hMG could do harm to patients with unrecognized autoimmune ovarian failure. Controlled evaluation is needed.

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Editorial Comment

The therapeutic excursions described by the correspondents are based on the hope that some subjects with hypergonadotropism may have a residual coterie of oocytes that can be saved and somehow jostled into action. Resistance or nonresponsiveness to gonadotropins in these cases might be due to circulating antagonists or some abnormality in a signal transduction pathway. The latter could be operative anywhere along the transmembrane pathway from a mutant gonadotropin receptor or a defective guanine nucleotide-binding protein (G-protein) to abnormalities in adenylate cyclase (AC) or cAMP-dependent protein kinase A (PKA). Mutations in these signaling proteins affecting their structure and aspects of their regulation are gradually emerging. Pandora's box has been opened by the recent publication of a mutation in a G-protein that results in continuous or constitutive stimulation of intracellular cAMP in tissues from subjects with the McCune-Albright syndrome (1). This somatic mutation leads to the clinical phe-

notype of precocious puberty, cafe-au-lait spots, and the real culprit—autonomously functioning ovarian cysts. The syndrome may have protean manifestations that seem to result from the ligand-independent activation of various endocrine target cells or tissues, including melanocytes. The postzygotic origin of this G-protein mutation, and its restriction to the G-protein-coupled receptor family, seems to account for its tissue distribution. A similar somatic mutation with autonomous adenylate cyclase activity has been described in the DNA of some growth hormone producing pituitary tumors and certain neoplastic thyroid tissue (2, 3). Overlooked in the excitement of an explanation for the enigmatic McCune-Albright syndrome was the fact that a similar but slightly different G-protein mutant had been described in some patients with Albright's Hereditary Osteodystrophy (AHO) just a year ago by Patten et al (4). This mutation is germ line in origin and associated with decreased tissue responsiveness to trophic hormones that act in a parallel fashion through the stimulation of AC and activation of PKA. Subjects with AHO have target organ unresponsiveness to parathyroid hormone (PTH) and demonstrate a high incidence of resistance to other trophic hormones. The latter is consistent with a fundamental defect that affects a common transmembrane response mechanism and is not limited to PTH. Such patients would be likely candidates to have a full complement of ovarian secretory elements (secretory ovarian failure) but would be unable to respond to gonadotropins because of their G-protein signaling defect. These investigations of G-proteins underline the need to study each of the genes that is involved in signal transduction and activation of transcription for pituitary gonadotropins. Several groups are working with the gonadotropin receptor genes, and others are looking at the multiple components of the AC gene system, including a cAMP response element binding protein that affects the final activation of target gene transcription. The bottom line is that some of the study subjects receiving gonadotropin-releasing hormone agonists, estrogens, and human menopausal gonadotropins, might benefit more from a little cAMP stimulation with a cAMP analogue or PKA therapy. This current decade of trawling for mutants in humans will continue to be challenging, but it has the potential to provide us with the biochemical basis for diseases such as premature ovarian failure where the majority of the clinical phenotypes are indistinguishable from each other. The basic heterogeneity, phenotypic spectrum, and evolution of disease as it occurs through somatic and germ line mutation should become more intelligible as these

mutations are revealed. The only pessimistic note is the potential number of mutant genes and potential number of mutants in each gene system. It is more than likely that future studies of G-protein coupled receptor gene expression will reveal even more elaborate mechanisms for intracellular signaling systems, which in turn increase the potential numbers of clinically relevant mutations. Each of the 26 subjects who participated in Dr. Larry Nelson's well-designed study could have 26 different mutations involving a plethora of known and orphan signaling genes. I can only pray to the "Great Geneticist" in the sky that he/she has not made it harder than we can think! Otherwise, the single curmudgeon clinician who insists that "I am not interested in how it works but only in how to treat it" may possess more of that uncommon commodity called common sense than the rest of us.

Paul G. McDonough, M.D., Editor, Letters

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A Simpler Technique for Reduction of Uterine Septum

To the Editor:

Valle et al. (1) reported on their experience with a nonhysteroscopic method of transcervical reduction of uterine septum. With the use of fluoroscopic guidance in the operating theater, concomitant with laparoscopic observation, they were able to successfully transect uterine septa using a modified Metz-enbaum scissor.

They claim that this approach has the advantage of minimizing instrumentation (I assume by not having to use a hysteroscope), a shorter operating time, decreased morbidity, reduced cost, and more consistent results. It is hard for me to believe that dragging fluoroscopic equipment into an operating theater and the necessary staff to perform this pro-