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### Chronic telogen effluvium: Potential complication for clinical trials in female androgenetic alopecia?

*To the Editor:* The study of Whiting (*J Am Acad Dermatol* 1996;35:899-906) describes a diffuse hair thinning in middle-aged women termed *chronic telogen effluvium* (CTE) with clinical features similar to female androgenetic alopecia (AGA). According to Dr. Whiting, one sees increased shedding and some diffuse thinning located all over the scalp and this hair loss occurs over a fluctuating time course of up to several years. Balding is not observed, and the thinning may not be obvious to anyone but the patient. Frequently, bitemporal frontal recession, at times severe, is also observed. Complicating the diagnosis in some patients is the coexistence of both CTE and AGA.

Taking into account the age group (30 to 60 years of age) of female patients in Dr. Whiting's analysis, the clinical features of pure CTE could easily be mistaken by many clinicians/investigators for mild to moderate female AGA, in which the prevalence of frontal recession<sup>1</sup> ranges from 13% to 37%, depending on the menopausal status. Fortunately, Dr. Whiting has also shown that the diagnosis of CTE can be confirmed and differentiated from AGA with the aid of horizontal sections of 4 mm punch biopsy specimens. One has to wonder whether percentages given in earlier reports<sup>1</sup> for bitemporal recession in female AGA include some misdiagnosed cases of CTE.

The existence of CTE complicates the clinical diagnosis of milder forms of female AGA. CTE in women has clinical importance not only for providing the correct cause and prognosis to the patient but also has potentially serious implications for investigations of new hair growth agents. Depending on the stage of CTE for a particular subject, the erroneous inclusion of a few or more subjects with CTE, in a study population thought to consist entirely of female AGA, may be enough to distort the clinical response/efficacy results and the perceived benefit of a therapeutic/investigational agent. In the active stage of CTE, the involved hair follicles would probably fail to respond to the investigational agent, which may cause a false-negative

result. In the recovery stage of CTE, the increased amounts of spontaneously regrowing hair might be interpreted falsely as a positive result. In this regard, one now has to look more closely at the efficacy results reported in trials for minoxidil solution 2% in female AGA<sup>2,3</sup> and wonder whether, here too, the study populations may have been contaminated with subjects who have CTE. Although AGA is generally considered etiologically to be the same disease in both male and female subjects, gender-specific differences were seen in the pivotal clinical trials for minoxidil solution 2%. Although there were certain limitations to these studies in terms of design features,<sup>2,4</sup> male patients with moderate degrees of AGA (Hamilton types III vertex, IV, and V) outperformed female patients as responders by almost 2 to 1 with the use of the Investigator Evaluation (physician global assessment) and Patient Evaluation (subjective improvement) grading scales.<sup>5</sup> Some authors<sup>3</sup> have even questioned whether any efficacy for minoxidil solution 2% in female subjects was demonstrated in these studies, which enrolled premenopausal women 18 to 45 years of age with mild to moderate (Ludwig types I and II) disease severity. Is it possible that the erroneous inclusion of more than a few subjects with CTE flawed (i.e., underestimated) the efficacy results of the female trials?

Given that CTE can cause confusion with mild to moderate female AGA, a clinical protocol must be extremely careful with regard to subject enrollment because these studies now generally include "middle-aged" women irrespective of menopausal status. Subjects with CTE, alone and in combination with female AGA, should be carefully excluded from therapeutic trials involving female AGA. Obtaining a 4 mm punch biopsy specimen for horizontal sectioning for each subject about to enter a study of female AGA, although not currently a routine part of the entry diagnostic evaluation, may now make good sense.

Seymour Rand, MD  
Dermatology Drug Development  
1515 Jefferson Davis Hwy.  
Arlington, VA 22202

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