Prevalence of premature ovarian failure in women with tuberous sclerosis complex

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Tuberous Sclerosis Complex (TSC) is an autosomal dominant tumor suppressor disorder characterized by hamartomas, or benign growths, in various organ systems. Inactivating mutations in either the TSC1 or the TSC2 gene cause most cases of TSC. Recently, the use of ovarian specific conditional knock-out mouse models has demonstrated a crucial role of the TSC genes in ovarian function. Mice with complete deletion of Tsc1 or Tsc2 showed accelerated ovarian follicle activation and subsequent premature follicular depletion, consistent with the human condition premature ovarian failure (POF). POF is defined in women as the cessation of menses before the age of 40. The prevalence of POF is estimated to be 1%, affecting a substantial number of women. Nonetheless, the etiology of most cases of POF remains unknown. Based on the mouse model results, we hypothesized that the human TSC1 and TSC2 genes are likely to be crucial for ovarian development and function. Moreover, since women with TSC already have one inactivated TSC gene, we further hypothesized that they may show a higher prevalence of POF. To test this hypothesis, we surveyed 1000 women with TSC belonging to the Tuberous Sclerosis Alliance, a national support organization. 182 questionnaires were analyzed for information on menstrual and reproductive function, as well as TSC. This self-reported data revealed 9 women (4.95%) with possible POF, as determined by menstrual history report and additional supportive data. The prevalence of 4.95% is much higher than 1% in the general population. Data from all women suggested other reproductive pathology associated with TSC such as a high rate of miscarriage (41.2%) and menstrual irregularity of any kind (31.2%). These results establish a previously unappreciated effect of TSC on women’s reproductive health. Moreover, these data suggest that perturbations in the cellular pathways regulated by the TSC genes are likely to be an important etiology of POF.

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