

ommended to provide a definitive diagnosis. The intriguing possibilities mentioned by Kent et al. are certainly in play, as is the more prosaic α -thalassemia trait.

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Postpartum Venous Thromboembolism

TO THE EDITOR: In their Image in Clinical Medicine, Zalts and Hayek (Dec. 18 issue)¹ describe a woman with postpartum venous thromboembolism. The patient was found to be heterozygous for a mutation in the gene encoding for 5,10-methylenetetrahydrofolate reductase (MTHFR). The authors suggest that the mutation was most likely the source of her susceptibility to hypercoagulation. However, a recent, large-scale, prospective study involving 66,140 participants did not show an association between a homozygous or heterozygous MTHFR genotype and the risk of venous thromboembolism.² The odds ratio for the development of venous thromboembolism was 1.01 for the heterozygous (C677CT) or homozygous (C677TT) genotype, as compared with the normal MTHFR genotype. Moreover, a heterozygous genotype was found in 41% of the population, in both the case and control groups, suggesting a much higher prevalence of the aberrant

genotype than of venous thromboembolism.² Therefore, in the patient described by Zalts and Hayek, the acquired risk factors (pregnancy and postpartum period, surgery, and reduced mobility), which were recently reviewed in the *Journal*,³ appear to be a more likely cause of venous thromboembolism than the observed mutation in the gene encoding MTHFR.

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Ending Propylthiouracil-Induced Liver Failure in Children

TO THE EDITOR: Graves' disease is treated with antithyroid drugs, radioactive iodine, or surgery.^{1,2} Propylthiouracil and methimazole are widely used in children as first-line therapy.^{1,2} Over the past 60 years of propylthiouracil and methimazole use, reports of propylthiouracil-related liver failure and death have accumulated.³⁻⁵ In contrast, this problem has not been reported with methimazole use in children.^{3,5}

Several observations can be made on the basis of the medical literature, adverse event reports from the Food and Drug Administration (FDA), and extensive data presented at a workshop at the Eunice Kennedy Shriver National Institute of

Child Health and Human Development on October 28, 2008, to discuss the safety of propylthiouracil use in children.⁵ Each year in the United States, 4000 pediatric patients with Graves' disease are treated with antithyroid drugs, with up to 40% receiving propylthiouracil over the past several years.⁵ Propylthiouracil-induced liver failure may occur in 1 in 2000 to 1 in 4000 treated children, but the number in whom reversible propylthiouracil-induced liver injury develops may be 10 times that range.⁵ However, the true extent of propylthiouracil-induced liver injury is unknown.⁵ Routine biochemical surveillance of liver function and hepatocellular integrity is not

viewed to be effective in managing the risk of liver failure.⁵

Although more children received methimazole than propylthiouracil during the periods in which propylthiouracil-induced liver failure has been reported,^{3,5} there are no reports of liver failure or liver transplantation in association with methimazole use in children.⁵ There are also fewer and less-serious adverse event reports in the FDA database for methimazole than for propylthiouracil.⁵

In 2007, more than 9000 prescriptions were written for propylthiouracil for use in children.⁵ It is estimated that more than 1000 pediatric patients are currently receiving propylthiouracil in the United States.⁵ It is clear that, at present, there is no good plan for managing the risk of hepatotoxicity in a patient receiving propylthiouracil, other than not using the drug.⁵ On the basis of recent data,⁵ we thus estimate that if propylthiouracil use continues at current levels, it is likely that propylthiouracil-induced liver failure requiring transplantation will develop in at least one child over the next few years.

Considering this estimate, we suggest that propylthiouracil should no longer be used as first-line treatment for Graves' disease in children. Alternative treatments should be considered for children who are currently taking propylthio-

uracil. In this way, it should be possible to end propylthiouracil-induced liver failure in children.

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Dr. Rivkees reports serving as an expert witness in endocrine-related legal cases. No other potential conflict of interest relevant to this letter was reported.

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