A baby boy born to apparently healthy parents had a bright red rash over his face within 2 hours after birth (Panel A). He also had clinical features consistent with trisomy 21, which was confirmed by karyotyping. The initial laboratory tests showed a hemoglobin level of 14 g per deciliter and a platelet count of 24,000 per cubic millimeter. An electrocardiogram at 4 weeks of age showed normal sinus rhythm, and the rash was reduced (Panel B). A complete blood count showed a white-cell count of 4500 per cubic millimeter with a normal differential count; the hemoglobin level was 8.8 g per deciliter, the platelet count 79,000 per cubic millimeter, the aspartate aminotransferase level 108 U per liter, and the alanine aminotransferase level 115 U per liter. Serologic testing by means of a multiplex bead assay (BioPlex 2200; Bio-Rad Laboratories) was strongly positive for SSA (Ro) and SSB (La) (for each test: antibody index units, >8; negative result is <1), confirming the diagnosis of neonatal lupus. By the time the patient was 6 months old, the rash had resolved without specific therapy (Panel C), and the levels of hemoglobin, platelets, and liver enzymes had normalized. The child’s mother had not received a diagnosis of any autoimmune disorder previously. After further questioning, she described having dry eyes for more than 1 year, which required the frequent use of artificial tears. She was referred to a rheumatologist and received a diagnosis of Sjögren’s syndrome. Maternal antibodies crossing the placenta can lead to the clinical manifestations of neonatal lupus. Mothers with only mild or no symptoms of autoimmune disease may be at substantial risk for the development of an overt autoimmune disorder, most commonly Sjögren’s syndrome or systemic lupus erythematosus. Any future children of these parents are at risk for neonatal lupus and congenital heart block.