Pravastatin for prevention of HELLP syndrome
A case report

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1. Introduction
The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) is regarded as particularly severe form of preeclampsia, causing adverse pregnancy outcome for both the mother and the fetus.\cite{1} Soluble fms-like tyrosine kinase-1 receptor (s-Flt) is involved in the pathogenesis by inactivation of vascular endothelial growth factor, resulting in angiogenic imbalance and endothelial dysfunction.\cite{2}

Pravastatin, a hydrophilic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase inhibitor, has been shown to decrease levels of circulating s-Flt in animals.\cite{3–6} Reassuring data on teratogenicity and promising results in preliminary clinical studies\cite{7–10} prompted us to use pravastatin in a patient with a history of 2 pregnancies that had been complicated by severe, early-onset HELLP syndrome.

2. Case
In her first pregnancy (2012), the 36-year-old patient was referred to our unit at gestational age (GA) 20+3 with epigastric pain, nausea, and vomiting. Apart from a well-controlled Hashimoto thyroiditis her medical history was noncontributory. The laboratory results were consistent with HELLP syndrome (Fig. 1): hypertension and proteinuria, not present initially, developed subsequently. Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and acute fatty liver of pregnancy were excluded. Obstetric ultrasound revealed an appropriate for gestational age (AGA) fetus with no obvious malformations; blood flow velocity waveform indices of the fetal and fetoplacental circulation were normal; the uterine arteries, however, had highly abnormal pulsatility indices and bilateral notching (Table 1). The maternal condition deteriorated and necessitated termination of pregnancy at GA 20+5 (female, weight: 330g, 13th percentile). She made a rapid clinical recovery and was discharged on day 1 after termination.

One year later, in her second pregnancy, she was referred for severe fetal growth restriction and highly abnormal Doppler indices at GA 20+2 (Table 1). Because of first-trimester vaginal bleeding acetylsalicylic acid (ASA) had been withheld. Maternal symptoms were absent, and laboratory results were normal. She was monitored as outpatient until GA 22+2, when blood flow indices in the ductus venosus deteriorated; in addition, she developed symptoms of HELLP syndrome. The diagnosis was confirmed by laboratory results (Fig. 1). Temporizing management was initiated after extensive discussion; however, intrauter-
The HOMA (homeostasis model assessment) was slightly elevated, a subsequent glucose tolerance test showed a marginally abnormal 2-hour blood glucose concentration. The patient received nutritional advice; she declined treatment with biguanide derivatives.

Screening for thrombophilia did not reveal major inherited or acquired disorders except for homocysteinemia for the MTHFR (methylene tetrahydrofolate reductase) mutation C677T. Repeated controls for antiphospholipid antibodies remained negative. However, d-dimers were mildly elevated in several analyses.

In 2015, then 39 years old, she miscarried at 8 weeks’ gestation; karyotyping revealed trisomy 22.

In early 2016, now 40 years old, the patient conceived again. She was commenced on prophylactic treatment with low-molecular weight heparin (LMWH) (enoxaparin 40mg once daily), ASA (100mg daily), and natural progesterone (400mg daily intravaginally). The preconception treatment with L-thyroxin (50μg daily), selen (200μg daily), myoinositol (1000 mg daily), and folic acid (2.5mg daily) was continued. Pravastatin (10mg daily) was started at GA 12. Institutional review board approval is not required for off-label use treatment. After extensive counseling about the medication, written consent was obtained from the patient. Close surveillance (clinical, laboratory, and ultrasound) was initiated. Throughout the entire course of pregnancy, she was asymptomatic, and her laboratory results remained within normal range. The obstetric ultrasound revealed adequate growth of a fetus without major malformations, and normal Doppler indices of the fetal, fetomaternal, and uteroplacental vessels (Table 1). Gestational diabetes developed in the third trimester and was controlled with insulin. At GA 37 +1, elective cesarean delivery was performed (male; 2920g, 31st percentile; Apgar scores 9/10/10 at 1, 5, and 10 minutes, respectively; umbilical artery pH 7.35). Both, patient and newborn, made an uncomplicated postoperative/postnatal course and were discharged on day 3.

### 3. Discussion

Pravastatin at a daily dosage of 10mg, commenced early in the second trimester, in addition to ASA and LMWH, resulted in an uncomplicated pregnancy and term delivery of an AGA healthy neonate in a patient with a history of severe, early-onset, recurrent HELLP syndrome.

Presently, a HMG-Co-A-reductase-mediated decrease in sFlt-1 synthesis is hypothesized to be the mechanism underlying the positive effect of pravastatin in preeclampsia; in addition, a rise in levels of circulating placental growth factor (PIGF) may contribute to the improvement of the proangiogenic profile and the reversion of sequelae of inflammation and endothelial dysfunction.\(^\text{[5,7,9]}\) The effect of pravastatin on soluble endoglin, another cofactor of vascular homeostasis involved in the pathogenesis of preeclampsia, is less clear, and may include an organ-specific response.\(^\text{[9]}\)

In contrast to preeclampsia, HELLP syndrome is characterized by hepatic and hematologic manifestations. Nevertheless, HELLP syndrome and preeclampsia share the same pathophysiology, and HELLP syndrome is considered a particular manifestation of preeclampsia, respectively.

We assume that the mechanism of action of pravastatin in HELLP syndrome is comparable to its effect in preeclampsia. The hepatic uptake of pravastatin may be of particular advantage in HELLP syndrome because 50% of the absorbed drug is lost by a first-pass effect.\(^\text{[11]}\)
To our knowledge, this is the first report of pravastatin in severe, early-onset, recurrent HELLP syndrome; the positive outcome justifies further clinical trials in women at risk of developing HELLP syndrome.

References

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