Hypertensive diseases in pregnancy have a frequency of 5% and are therefore one of the most important conditions in obstetrics. The mildest form is pregnancy-induced hypertension, in combination with proteinuria the diagnosis of preeclampsia is established. Today, the complication of true eclampsia (convulsions, neurological dysfunction) can be avoided in most cases. HELLP syndrome is a severe variant of preeclampsia, the term abbreviating the characteristic features (hemolysis, elevated liver enzymes, low platelet count).

The pathogenesis of preeclampsia/HELLP syndrome is still not fully understood. According to current knowledge, there are four major dysfunctions that predispose to the disease: 1. Reduced placental perfusion, 2. Maternal metabolic disease or thrombophilia, 3. Immunologic reactions between maternal and fetal tissue, 4. Genetic factors. Familial clustering of preeclampsia/HELLP syndrome is well-known but the underlying genetic links remain to be identified. Since intrauterine growth restriction due to placental insufficiency is closely related to the preeclampsia complex, genetic studies should at best address all conditions that are associated with placental ischemia. Better knowledge of the responsible genetic factors has important implications for the development of causal therapies and prevention, for medical care and genetic counseling of affected families.

A collaborative project together with the Department of Obstetrics and Gynecology has been initiated in the early 2000s aiming at the clinical and molecular characterization of more than 1000 women with a history of preeclampsia/HELLP syndrome. For this project two resident physicians of the Department of Obstetrics and Gynecology (Dr. Peruka Neumaier-Wagner, Dr. Sabine Mütze) were exempted from clinical work for two years each. The patients were largely recruited from the German self support group for hypertensive diseases in pregnancy and prospectively over several years (until 2003) in the department of obstetrics. The patients provided information about their disease and pregnancy history along with the consent to have their medical files reviewed. Blood samples for genetic studies were collected from 500 index patients, and from many fetuses of affected pregnancies and additional relatives. If available, morphological data of the placenta in affected pregnancies were retrieved and further studies initiated together with the Institute of Anatomy.

We analyzed the clinical phenotypes and recurrence risks in preeclampsia/HELLP syndrome performed candidate gene analysis and association studies. We found that neither the maternal nor fetal E474Q mutation of the LCHAD gene plays a role for the development of HELLP syndrome. The same applied to the 4G/5G polymorphism of the plasminogen activator inhibitor 1 (PAI 1) gene. By analysis of genetic thrombophilia factors, the presence of a factor V Leiden mutation inferred a higher risk to develop HELLP syndrome, while this was not observed for polymorphisms of the prothrombin gene (20210G>A variant) or the MTHFR gene (677C>T variant). In addition, we did not find an association of preeclampsia/HELLP syndrome with polymorphism of the AGT gene, but identified the pathogenic L43F mutation in a patient affected by severe HELLP syndrome with intrauterine death. In pregnancies with reduced placental perfusion and intrauterine growth restriction we analyzed the growth factor genes P1GF, Flt, IGF-I and IGF-IR but did not detect mutations. The results of our studies were mostly published between 2007 and 2011.

In 2014, a new collaborative study was agreed with the Institute of Anatomy and Prof. Rath from the Department of Obstetrics and Gynecology based on the observation that an altered Nrf2-Keap-1 pathway causes placental perfusion abnormalities in mice. Analysis of these genes in patients with preeclampsia/HELLP syndrome will clarify their role in humans. A START grant support has been submitted in July 2014.

For the working group: Sabine Rudnik-Schöneborn (September 2014)