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In this thesis anticoagulant and antiplatelet treatment options during pregnancy are examined to prevent placenta mediated pregnancy complications, including hypertensive disorders of pregnancy (HD) in high risk populations. Hypertensive disorders of pregnancy is an umbrella term for pregnancy induced hypertension, preeclampsia, eclampsia and HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets). The women we examined had an adverse obstetrical history of placenta mediated pregnancy complications and/or an underlying disease increasing the risk for pregnancy complications, like systemic lupus erythematos. Moreover, cardiovascular risk factors in women with thrombophilia after HD is examined, as well as a relation between HD and Alzheimer's disease.

In the Introduction, risk factors, preventive strategies, short- and long-term outcomes of HD and the outline of this thesis are described.

In Chapter 1 we describe secondary outcomes of a randomized controlled trial (RCT): the FRUIT-RCT. We investigated whether low-molecular-weight heparin (LMWH), when added to low-dose aspirin, influenced fetal growth and flow-velocity in uterine and umbilical arteries. The FRUIT-RCT included 139 women with a previous delivery before 34 weeks gestation with HD and/or a small-for-gestational-age (SGA) infant and inheritable thrombophilia. Ultrasound measurements were performed at 22–24, 28–30 and 34–36 weeks gestation. This specific population has an impressively high risk both for neonatal SGA (30%) and for decreased flow-velocity within the uterine artery (48%). We concluded that the addition of LMWH to aspirin did not influence either fetal growth and umbilical artery flow-velocity over time nor uterine artery flow-velocity.

In Chapter 2 we investigated in a cohort study disease activity around and during pregnancy and pregnancy outcome in women with systemic lupus erythematous (SLE) taking their antiphospholipid antibody status into account. Moreover, differences between first and consecutive pregnancies and number of live births were examined. We included all ongoing pregnancies (>16 weeks gestation) of SLE patients receiving joint care from rheumatologists and gynecologists in two tertiary centers in the Netherlands between 2000–2015. From 96 women (84% Caucasian), 144 pregnancies were included. The median SELENA–SLE(P)DAI score was 2 before (<6 months), during and after pregnancy (<6 months) and flare rates were 6.3%, 20.1% and 15.3% respectively. HD, intrauterine fetal death (IUFD), preterm birth and SGA infants occurred in 18.1%, 4.1%, 32.7% and 14.8% respectively. Only HELLP-syndrome occurred more often in women with SLE and antiphospholipid syndrome (APS) compared to SLE women with or without antiphospholipid antibodies. Pregnancy complication rates were similar in first and consecutive pregnancies and half of the women did not experience any pregnancy complication during their studied reproductive period, whereas 42.7% developed a complication during all pregnancies. Mean number of pregnancies was 2.4 and live births 1.7. In conclusion, in a multidisciplinary monitored SLE population with low disease
activity, maternal and perinatal complications were nearly equally distributed between women with SLE with or without antiphospholipid antibodies or APS. This was irrespective of antiphospholipid antibody status and irrespective of first and consecutive pregnancies. We should use this information for patient counseling.

In Chapter 3 we related the use of aspirin and/or LMWH to pregnancy complications in women with SLE and primary APS. We studied 184 ongoing pregnancies, in which women had their check-ups on both the obstetric and rheumatology department in one of two Dutch tertiary centres between 2000-2015. LMWH and aspirin was prescribed in 15/109 SLE women without antiphospholipid antibodies (aPL), 5/14 with aPL, 11/13 with APS, 45/48 with primary APS. Main complications in the four treatment groups (no anticoagulant treatment, aspirin, LMWH, aspirin and LMWH) included HD (9.4%, 23.3%, 50%, 18.4% respectively) and preterm birth (16.7%, 34.3%, 75%, 36.8% respectively). The maternal and perinatal outcomes in the complete cohort showed that the subgroups with anticoagulant treatment experienced more maternal and perinatal complications compared to those without anticoagulant therapy. The overall incidence of maternal and perinatal complications was high, irrespective of treatment group and despite low SLE disease activity in the majority of the population within six months before pregnancy.

In Chapter 4 we describe the protocol of an individual patient data meta-analysis (IPDMA) for LMWH intervention for the prevention of recurrent placenta-mediated pregnancy complications. Placenta-mediated pregnancy complications include HD, late pregnancy loss, placental abruption, and SGA infants. We conducted a systematic review to identify RCT's with LMWH intervention for the prevention of recurrent placenta-mediated pregnancy complications. Investigators and statisticians representing eight trials met to discuss the outcomes and analysis plan for an IPDMA. The goal of the IPDMA is a thorough estimation of treatment effects in patients with prior individual placenta-mediated pregnancy complications and exploration of which complications are specifically prevented by LMWH.

In Chapter 5 the results of the IPDMA are presented. A systematic review was performed in May, 2013, which identified eight eligible randomised trials done between 2000 and 2013 of LMWH to prevent recurrent placenta-mediated pregnancy complications. We analysed data from 963 eligible women in eight trials: 480 randomly assigned to LMWH and 483 randomly assigned to no LMWH. Participants were mostly white (88%) with a mean age of 30.9 years and 42% had thrombophilia. The inclusion criteria were preeclampsia, placental abruption, SGA infant, pregnancy loss above 16 weeks or two pregnancy losses above 12 weeks. The primary outcome was preeclampsia below 34 weeks, severe preeclampsia, SGA infant, pregnancy loss above 20 weeks or placental abruption. In the primary analysis, LMWH did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications (LMWH 14% versus no LMWH 22%). We noted significant heterogeneity between single-centre and multicentre trials. In subgroup analyses, LMWH in multicentre trials reduced the primary outcome in women with previous abruption but not in any of the other subgroups.
of previous complications. We concluded that LMWH does not seem to reduce the risk of recurrent placenta-mediated pregnancy complications in at-risk women.

In **Chapter 6**, we examined adherence rates in women to whom aspirin is prescribed due to their increased risk for pregnancy complications. Women between 24 and 36 weeks gestation with an indication for aspirin use during pregnancy were invited for this study. A survey was used which included two validated questionnaires, the simplified medication adherence questionnaire (SMAQ) and the Beliefs and Behaviour Questionnaire (BBQ). Indications for aspirin use during pregnancy were previous HD, fetal growth restriction, IUFD or current maternal disease. Non-adherence rates according to the SMAQ and BBQ were 46.3% and 21.4% respectively. No differences in demographic background or obstetrical characteristics between adherent and non-adherent women could be demonstrated. This study showed that adherence for aspirin in this high-risk population cannot be taken for granted. Surprisingly, despite the clear short term to prevent recurrent pregnancy complications, the non-adherence rates in pregnant women are comparable with the non-adherence rates for aspirin in the non-pregnant population. In daily practice, the doctor should motivate their patients to take their aspirin.

In **Chapter 7**, we examined whether aspirin resistance is associated with recurrent HD. We hypothesized that the aspirin did not work properly in women with recurrent HD. Aspirin resistance was tested using three complementary tests: PFA-200, VerifyNow® and serum thromboxane B₂ (TXB₂). Thirteen of 24 women with recurrent HD and 16 of 24 women without recurrent HD participated. The prevalence of aspirin resistance in the whole group was 34.5% according to the PFA-200, 3.4% according to the VerifyNow® and 24.1% according to TXB₂. The prevalence of aspirin resistance by any test was 51.7%. Aspirin resistance per individual test did not differ between women with and without recurrent HD. Aspirin resistance measured by any test occurred more frequently in women without recurrent HD irrespective of LMWH limitations of the study was that it was performed up to 16 years after the pregnancy. In conclusion, we could not find a relation between recurrent HD and aspirin resistance per test, measured up to 16 years after pregnancy. On the contrary, complementary aspirin resistance measurements were encountered more frequently in women without recurrent HD.

In **Chapter 8**, we present the protocol of the RADAR study: Resistancy of Aspirin During and After Pregnancy. This longitudinal cohort study is undertaken to investigate the above mentioned limitation and assess the consistency of aspirin resistance during and after pregnancy. It is unknown whether aspirin resistance changes over time and how pregnancy affects aspirin resistance. Aspirin resistance is measured in the first, second and third trimester of pregnancy and at least three months postpartum. Four complementary tests are used: PFA-200, VerifyNow®, Chrono-log light transmission aggregometry and serum thromboxane B₂. 23 women participated in this study. The results are expected during the first half of 2017. The results will support us with the interpretation of the results of Chapter 7 on the possible relation between aspirin resistance and HD. Adding the knowledge of the
present study with the use of several complementary tests facilitates comparison with other studies and thus might give more insight if aspirin resistance is a factor of importance in the treatment to prevent HD.

In Chapter 9 the prevalence of cardiovascular risk factors were examined in women with inheritable thrombophilia 8-19 years after early-onset HD, with or without recurrent HD. We included 22 women: 11 women with recurrent HD and the other 11 women without recurrent HD. Nearly three-quarters of the women had an higher prevalence of cardiovascular risk factors, irrespective of single or recurrent HD. Women with recurrent HD did have higher systolic and diastolic blood pressure and albumin creatinine ratio compared to women with single HD. This is similar to other studies examining cardiovascular risk factors in women with a history of HD in which their thrombophilia status was unknown.

In Chapter 10 we hypothesized that women who have had a pregnancy complicated by HD are at increased risk of Alzheimer’s Disease later in life. We performed a nested cohort study in 251 women with Alzheimer’s Disease and 249 women without Alzheimer’s Disease. Neither a significant difference between women with and without Alzheimer’s Disease in a history of HD, including pregnancy induced hypertension (12.7 vs 25.9% respectively) was found. Nor an association between Alzheimer’s Disease and preeclampsia (2.9% in women with Alzheimer’s Disease versus 3.1% in women without Alzheimer’s Disease). We concluded that a reported history of HD appears not to be associated with Alzheimer’s Disease later in life. These findings suggest (at least partly) different pathophysiological pathways of cerebrovascular damage associated with HD and those related to Alzheimer’s Disease.

In the discussion, the results of this thesis are discussed and recommendations for clinical practice and implications for future research are debated and summarized hereafter. First, the IPDMA, only found a beneficial effect of LMWH in women with previous placental abruption, which is not in line with the results of individual RCT’s which are included in this IPDMA. Limitation of the IPDMA is the use of composite in- and exclusion criteria. Second, to examine the effect of LMWH in women with SLE, a RCT is needed. Third, adherence for aspirin is a subject for patient counselling. Moreover, the hypothesis that aspirin resistance is involved in the occurrence or recurrence of HD seems plausible, it might be possible that the right device/test to examine aspirin resistance has not been developed yet. Furthermore, to examine the role of thrombophilia itself on the risk to develop cardiovascular risk factors after HD can be examined in the near future, since data of a similar population without thrombophilia is currently collected. Finally, to examine if there is a relation between Alzheimer’s Disease and HD, and to eliminate the potential recall bias, a prospective cohort study is needed.