Fetal brain damage is an important cause for (mild or severe) neurodevelopmental impairments in infancy and childhood. The progress in imaging techniques in the last decades has enabled clinicians in prenatal medicine to screen for and diagnose brain damage before birth, for example in fetuses at risk for brain damage. Advanced multiplanar fetal brain ultrasound (neurosonography) and magnetic resonance imaging (MRI) of the fetal brain have proven their value for the diagnosis of brain anomalies. It is, however, not yet clear which imaging modality is most suitable to depict (subtle) acquired anomalies, that may be visualized in cases at risk for (mild) brain damage.

A prospective, observational study was therefore conducted, to examine findings on fetal brain ultrasound and MRI in fetuses at risk for acquired brain anomalies. The examinations were performed repeatedly, before and after birth, and the infants were followed with neurodevelopmental examinations until 5 years of age.

In Chapter 1 we provided a general introduction about (prenatal) risk factors for and neurodevelopmental consequences of brain damage; the imaging modalities; and the developmental examinations useful in the assessment of possible effects of acquired fetal brain damage. The primary question of this thesis was to study the additional value of multiplanar neurosonography and fetal brain MRI to the standard assessment using axial ultrasound planes only.

The results of this prospective, multicenter Fetal Brain Imaging (FBI-)study are elucidated in Chapter 2. Fifty-six fetuses were examined and in 39 of them all three fetal imaging techniques (standard axial ultrasound planes, neurosonography and
MRI) were available. Mild acquired anomalies (such as periventricular echogenicity changes, mild bleeding) were found more often on neurosonography compared to axial ultrasound planes and the equivalent signal intensity changes on MRI. None of the examined children had neurodevelopmental delay at two years of age, however, twenty out of the 56 children had (mildly) abnormal scores on (one of the) developmental, sensory profile, and/or linguistic examinations.

In case of a high risk of mild acquired fetal brain damage, we recommend assessment of the fetal brain by means of neurosonography instead of MRI. Due to the limited amount of participants in the FBI-study, it was not possible to reliably relate findings on prenatal imaging to neurodevelopmental outcome in infancy.

In Chapter 3 we analyzed the high number of women declining FBI-study participation. Forty-seven/104 (45%) of the invited women did not want to participate. The major reason for study declination was MRI related, in 41%. Only 34/57 women who did agree to participate, underwent the fetal MRI examination. We compared this acceptance rate to women who were offered a fetal MRI examination for clinical reasons (a suspected congenital (brain) anomaly on ultrasound). Nearly all women in this group (43/44) underwent the fetal MRI examination. Interestingly 5 of the 34 research cases declined to undergo the neonatal MRI examination due to the anxious or unpleasant experience during the fetal MRI examination. We concluded that pregnant women consider fetal MRI more burdensome than professionals may realize. This may be a stumbling stone in future research with fetal MRI.

Women who underwent trauma during pregnancy were the subject of Chapter 4 to 7. Chapter 4 and 5 describe the results of two prospective studies of fetal motility (Chapter 4) and histological assessment of the placentas (Chapter 5) after trauma during pregnancy.
Additionally, two retrospective analyses about obstetrical outcome (Chapter 6) and long-term health- and developmental outcome (Chapter 7) in an 11 year cohort of fetuses exposed to maternal trauma in pregnancy were described.

In Chapter 4 we prospectively studied the motility of sixteen fetuses exposed to maternal trauma. This study was carried out because fetal motility represents the spontaneous activity of the central nervous system and as such can be used to evaluate its functional integrity.

Motility was analyzed by means of three one-hour ultrasound observations, at 2-8 hours, 24-72 hours and >72 hours after a trauma took place. We focused on differentiation into specific movement patterns, quality and quantity of general movements and compared the outcomes to a normal population.

Abnormal differentiation was encountered in 2/16; 2/14 and 0/16; abnormal quality in 2/16; 3/14 and 6/16; and abnormal quantity in 6/16, 9/14 and 9/16 at T1, T2 and T3 respectively. All of the infants had normal neurological outcome at two years of age. The changes in motility support the hypothesis that trauma may influence the functional integrity of the central nervous system, although no neurological sequelae were present at 1 year.

Histological examination of the placentas of women exposed to trauma in pregnancy was performed in Chapter 5. Significantly more placental pathology was found after trauma compared to placentas from uneventful pregnancies, in a modest number of women. The pathological findings consisted mainly of retroplacental hematomas, intervillous thrombi and chorioamnionitis. Neurological follow-up at one year of age was normal in all infants.
The presence of intervillous thrombi and retroplacental hematomas reflects hypoxic events and/or fetomaternal hemorrhage, which may explain the high prevalence after trauma.

The obstetrical outcome of pregnancies complicated by trauma between 1995 and 2005 was studied in Chapter 6. We encountered a considerable number of trauma admissions (at any gestational age) at Amsterdam UMC, location VUmc in this period of time; 10 per 1000 deliveries. In the vast majority (92%), there were no or mild maternal injuries. After trauma exposure, women had obstetrical complaints in 40% (mainly uterine contractions (30%)). Abnormal diagnostic tests (e.g. CTG, ultrasound) were present in 8%. A composite adverse perinatal outcome (defined as intrauterine fetal death, placental abruption, preterm delivery and/or birth weight <10th percentile) was found in 17/80 cases, ten of whom were preterm births. Severe injuries were predictive of a composite adverse outcome. Type of trauma, obstetrical symptoms and/or abnormalities on diagnostic examinations were not. These findings support recent international literature on this subject and endorse a less defensive set-up of care (a brief fetal assessment instead of 24 hour admission) for the pregnant trauma patient without injuries.

In Chapter 7 we studied the long term effects of maternal trauma in pregnancy on the neurobehavioural development of children between 6 and 18 years (cases), compared to children whose mother had an eventless pregnancy (controls). Twenty-one and 12 percent of the cases and controls, respectively, returned the questionnaires about general health, motor development and educational level, and concerning behavioural development through the validated Dutch version of the Child
Behavior Checklist. We found no differences in health, motor development, educational level and Child Behaviour Checklist between the cases and controls, except for more hospitalization in the cases ($p = 0.009$) and a trend for increased externalizing behaviour problems. Due to the limitations of our study (poor response rate, risk of response bias), confirmation is needed from larger prospective studies.

Another risk factor for fetal brain damage, congenital cytomegalovirus (CMV) infection, was addressed in Chapter 8. Specifically early maternal primary infections have been described to carry the highest risk of fetal brain damage. Signs of congenital CMV infection can be found on prenatal ultrasound examinations (by means of, amongst others, microcephaly, ventriculomegaly, intracerebral calcifications, hepatosplenomegaly, echogenic bowels), or may present after birth (for example with microcephaly, hepatosplenomegaly, thrombocytopenia). Maternal serology is regularly tested for CMV infection because of a suspected fetal ultrasound anomaly in clinical practice. Chapter 8 describes five cases in which a primary CMV infection in pregnancy was considered unlikely based on serological testing, however after birth a congenital CMV infection appeared to be present. By analyzing the pitfalls in these cases, important lessons are: the importance to store first trimester maternal serum in laboratories, to enable serological testing at later stage. Serological testing of first trimester serum enables timing of an infection. Furthermore, it is important for clinicians to realize that besides primary infections, also non-primary infections can cause fetal brain damage (by reactivation of the already present strains or re-infection with a new CMV strain).
Chapter 9 presents a description of the execution, advantages and disadvantages and safety of neonatal cranial ultrasound. There is no evidence that cranial ultrasound is damaging to the neonate. Nevertheless, it is wise to limit the examination time and to use the lowest possible Thermal and Mechanical index values.

The thesis ended with a reflection on the study results in the General Discussion (Chapter 10). Additionally this chapter contains recommendations for clinical practice as well as future perspectives.