SUMMARY

Historically intrapartum asphyxia has been regarded as a major cause for abnormal neurological outcome, e.g. cerebral palsy. There is substantial evidence that the majority of hypoxic-ischemic events have occurred before birth. This growing insight supports the necessity to perform studies including close monitoring of fetal and neonatal parameters and adequate neurological follow-up.

For this thesis fetal sonographic brain imaging in pregnancies threatened by preterm birth were studied. Evolution of echogenicity changes in the fetal brain were examined. Basal fetal heart rate and its variation was investigated and related to brain echogenicity changes. General movements of the fetus were related to the brain echogenicity changes and their evolution to after birth was described. Placental histology was compared with the brain echogenicity changes. The outcome of the fetuses with the various brain echogenicity changes was described up to 6 years of age.

The population of 124 fetuses was studied at the Tygerberg Hospital, Belville, South Africa.

In Chapter 1 the general introduction discusses the background and rational of the study and provides an overview of the current knowledge on prevalence, risk factors and pathophysiology of perinatal brain injury and methodology of brain ultrasound imaging in the fetus. It describes the outline of the thesis.

Chapter 2 reports the prevalence of echogenicity changes in three areas of the fetal brain vulnerable for hypoxic-ischaemic or infectious injury. The population studied consisted of 124 fetuses of pregnancies at risk for preterm birth because of either hypertensive disorder of pregnancy (HD) (n = 64) or preterm labour (PTL) (n = 60) between 26 and 34 weeks gestational age (GA). At inclusion 66% of all fetuses had echogenicity changes in one or more areas of the brain. They were present in the periventricular white matter (PVE) in 52%. In the intraventricular area (IVE) in 18% and in the deep grey matter of the basal ganglia and thalami (BGTE) in 28%. There was overlap in echogenicity changes in the three brain areas in 35/124 fetuses, and only in 38 fetuses no changes were found. Echogenicity changes were found during the whole gestational age (GA) period (26-34 weeks) and were equally distributed over pregnancies with HD or PTL. In the 25 fetuses in whom with serial ultrasound examinations could be performed before delivery, all three brain areas showed a dynamic process of appearance, persistence, increase or disappearance of echogenicity changes. Of the PVE with echogenicity changes that exceeded in echodensity that of the choroid plexus (PVE Grade IB), at least 50% persisted after delivery. At least 38% of the IVE and 32% of the BGTE persisted after delivery.

Chapter 3 reports a case-control study on 20 fetuses with moderate PVE (Grade IB-II), IVE (Grade II-III) and/or BGTE (localized) matched for GA, fetal growth restriction (fetal abdominal circumference < 10th percentile), and maternal clinical disease (8 HD and 12 PTL) with 20 fetuses without echogenicity changes. Computer analysis of fetal heart rate traces was performed using a Sonicaid 8000 system (Sonicaid Ltd, Chichester). Fetal heart rate parameters like baseline heart rate, episodes of high and low heart rate variation, long term variation and short term variation were identified, and plotted within the 2.5th, 50th and 97.2th percentiles lines of a normal population.
No statistical differences were found for any of the fetal heart rate parameters between fetuses with and without moderate echogenicity changes.

No difference in anti-hypertensive or betamethasone medication use was found. Both for the cases and the controls the heart rate variation distribution was significantly lower than for the normal population ($\chi^2$-squared test; $p < 0.001$), illustrating the compromised status of this high risk population.

In Chapter 4 the quality of general movements (GMs), and GM parameters (amplitude, speed and complexity) were related to the presence of mild and moderate echogenicity changes in the brain in 121 fetuses. GMs were classified as abnormal in 58% of the fetuses. The variability of the amplitude of GMs was most frequently reduced (96%), while both the speed and the complexity were affected in 59%. As expected, abnormal GMs were significantly more frequent in the HD group ($n = 63$) compared to the PTL group ($n = 58$) ($p = 0.015$), in oligohydramnios versus normal amniotic fluid ($p = 0.002$), and showed a positive trend for small for gestation age fetuses vs. appropriate for gestational age fetuses ($p = 0.058$). The prevalences of mild (39%) and moderate (31%) echogenicity changes (in the three areas combined) were not significantly different in the HD and PTL group.

The predictive values of abnormal GMs were calculated for moderate echogenicity changes (PVE Grade IB-II, IVE Grade II-III, BGTE locally increased) in the three brain areas separately and combined. A high negative predictive value and a good sensitivity of GMs for moderate echogenicity changes (0.73 and 0.65 respectively), especially for PVE (0.96 and 0.85 respectively) were found. The specificity of GMs for moderate echogenicity changes was, however, low.

Chapter 5 reports on GM quality in the perinatal period and its relation to echogenicity changes in the brain. In 94/124 cases, GMs and the brain were assessed both before and in the week after delivery. Fetal GMs were abnormal in 64%, normalizing in 68% within 7 days after birth. Fetal GMs were significantly related to postnatal GMs ($p = 0.045$). Moderate fetal brain echogenicity changes and clinical parameters were not significantly related to neonatal GMs.

Chapter 6 reports on the relation between placental histology and echogenicity changes in the fetal brain. From 77 fetuses the placenta was retrieved after delivery and examined macroscopically and microscopically. The pregnancies were complicated by HD in 42 and by PTL in 35. Of the placentas 79% showed uteroplacental hypoperfusion, inflammation, or a combination. Brain echogenicity changes were present in 73% of the fetuses (44 mild, 29 moderate). Moderate brain echogenicity changes were equally distributed over cases with uteroplacental hypoperfusion and inflammatory features in the placenta. PVE Grade IB was always associated with placental pathology. The sensitivity and negative predictive value of placental pathology for moderate echogenicity changes were high (0.91 and 0.88 respectively), while the specificity and positive predictive value were low (0.27 and 0.34 respectively).

Normal placental histology predicted no or mild echogenicity changes, supporting the view that the latter are physiological. Placental pathology was always present in cases with PVE Grade IB, presumed to represent mild or early forms of white matter injury.

In Chapter 7 the outcome of the studied fetuses is presented. The neonates of the studied population had a median GA at birth of 31 weeks (range 26-43), perinatal mortality was 12.5% and an additional mortality in the first year was 6.5%. At 1 year
corrected age and at 2 and 6 years basic neurological examinations and Griffiths Mental Developmental Scales (GMDS) were performed. A composite outcome was defined as normal or abnormal (death or a developmental deficit defined as cerebral palsy, bilateral sensory neural deafness requiring hearing aid, blindness, and/or a abnormal GMDS assessment). Of the 101 surviving infants 89% were examined at 1 and 2, and 67% at 6 years of age. The neurodevelopmental outcome was abnormal in 24/124 (19%). Fetal moderate IVE were related to cerebral palsy at 6 year.

Neonatal moderate IVE were related to an abnormal GMDS at 2 years, cerebral palsy at 2 and 6 years, and to the composite outcome.

Of the pregnancy characteristics (maternal age, race, smoking habits, gestation/parity, presence of HD, PTL, prescribed medication, fetal growth and umbilical artery Doppler indices) only a reversed or absent end diastolic flow in the umbilical artery was related to the composite outcome. Of the neonatal characteristics (GA at birth, birth weight, Apgar scores if < 7 at 5 minutes, delivery mode, gender, duration of artificial ventilation, sepsis, major surgery, and seizures/meningitis) GA at birth, birth weight, Apgar scores < 7 at 5 minutes, and seizures or meningitis were related to composite outcome.

In the multiple regression analysis only gestational age was related to composite outcome (p = 0.005). Infants having moderate echogenicity changes after birth, but none before, had the highest risk of abnormal composite outcome (55%). Fetal moderate echogenicity changes did not relate to neurodevelopmental outcome or composite outcome (fetal, neonatal death or abnormal neurodevelopmental outcome), underlining the importance of adaptive mechanisms and plasticity in the immature fetal brain. GA at birth was the main predictor of composite outcome.

Chapter 8 comments on the findings of the various studies of this thesis and reflects on possible explanations. This prospective study in a large population of pregnancies complicated by either HD or PTL demonstrated in two thirds echogenicity changes in the fetal brain. The mild echogenicity changes in the periventricular white matter, the ventricular area, and basal ganglia/thalami were frequent in this high risk population. Some of these echogenicity changes probably represent normal maturational phenomena or at the most mild and/or transient injury. The moderately increased echogenicity changes in the three areas, especially those that persist after birth are likely to represent mild or early stage (transient) injury. Interpretation of fetal echogenicity changes should be performed with caution, evaluating Grading and extent and preferable after serial examination.

Normal GMs were associated with absence of echogenicity changes. Although of value for the evaluation of the actual fetal condition, GM assessment did not identify fetuses with moderate echogenicity changes in the three regions of interest.

Similarly, cardiotocography in the preterm period can clearly demonstrate low heart rate variability depicting the compromised status of the fetus, but computerized monitoring failed to identify fetuses with moderate echogenicity changes in the three brain regions of interest.

Pathological placental findings were found in 79% and always present in cases with PVE Grade IB, confirming our hypothesis that moderate PVE represents mild or early stage WM injury. This study additionally confirmed the presence of both utero-placental hypoperfusion and inflammatory changes in placentas of fetuses from HD.
Fetal moderate echogenicity changes did not relate to abnormal neurodevelopmental outcome and perinatal mortality after adjusting for GA at birth. Based on recent literature and the results of this study, it seems wise to refrain from acting upon a single fetal brain examination.

Our overall study results support that perinatal clinical parameters are helpful for prediction of outcome in high risk fetuses and that serial brain examinations before and after birth may contribute to understanding the reactions of the developing brain to unfavourable circumstances. However, screening for acquired brain injury in the third trimester of high risk pregnancies still needs to be developed. The importance of interdisciplinary collaboration between specialists active in the field of surveillance of the fetus and preterm neonate is emphasised.