Fetal growth restriction
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 7

General discussion
This thesis comprises studies on fetal growth restriction (FGR) from the prenatal period to school age with the emphasis on prenatal and neonatal circulatory adaptations and neurological outcome. Our first aim was to assess prenatal cardiac function in FGR. In Chapter 2, therefore, we measured longitudinal annular displacement (LAD) in growth-restricted fetuses. Our second aim was to determine whether prenatal ultrasound measurements of growth-restricted fetus are associated with early and late neonatal distribution of circulation and neurological functioning. Doppler pulsatility indices (PIs) of the fetal vessels were assessed and we compared them with neonatal multisite near-infrared spectroscopy (NIRS) (Chapter 3) and general movements (GMs) (Chapter 4). Our third aim was to investigate functional outcome at school age of small-for-gestational-age (SGA) children born very preterm on the one hand, and moderately preterm-born to full-term infants on the other hand. To this end, we performed an extensive follow-up study at the age of seven and eight years of children born SGA (Chapters 5 and 6).

Cardiac function in FGR

In Part I we present a study on cardiac function in FGR with prenatal ultrasound. We found that left, right, and septal LAD measured with spatiotemporal image correlation (STIC) was reduced in FGR in comparison to age-matched controls (Chapter 2). Cardiac LAD, commonly used in adult echocardiography, is a parameter that measures myocardial motion. In 2001, Carvalho et al applied LAD to fetal echocardiography and found it to be a useful tool to assess systolic and diastolic function of the fetal heart for clinical purposes. In FGR, the heart is a central organ in the adaptive mechanisms following placental insufficiency and it can already display profound structural and functional changes prenatally. In a previous report LAD was decreased in a group with severe FGR. In FGR, however, LAD was only measured online with motion mode (M-mode). This has several disadvantages, one being that LAD measurements are less precise due to fetal movements. Another method, spatiotemporal image correlation (STIC), allows LAD to be measured offline by using four-dimensional (4D) ultrasound analysis. We hypothesized that STIC is the better method to measure cardiac function. To test this hypothesis, we compared the online M-mode of measuring LAD in FGR with the offline STIC method (Chapter 2). The STIC method proved to be better than the online M-mode in detecting reduced cardiac motion. The disadvantage of using STIC, however, is that the clinician has to invest time in learning to use the technique and how to analyze it. The latter method might, therefore, be better suited for use in a research setting. If the clinician is able to invest in learning how to use the STIC technique, the advantage is that it is a useful aid in clinical decision-making. The offline technique is not only of value in FGR management, but adds in the clinical approach of various fetal cardiac anomalies. STIC allows clinicians to store a 4D image of the fetal heart to be
viewed whenever the need arises. This enables clinicians to quietly reexamine a fetal cardiac defect after clinic hours and, if need be, consult a colleague about the anomaly with the 4D image of the fetal heart at hand. We recommend implementing STIC as part of clinical practice of obstetricians involved in FGR and fetal assessment of potential congenital cardiac defects.

**Prenatal predictors of neonatal distribution of circulation**

In Part II we present a study on prenatal Doppler measurements and its associations with neonatal circulatory consequences of FGR (Chapter 3). Low middle cerebral artery (MCA) PIs and low cerebroplacental ratio (CPR), indicating brain sparing before birth, were strongly associated with a low cerebrorenal ratio after birth, indicating higher postnatal blood supply to the cerebrum than to the renal region. We speculated that if brain sparing is present in fetal circulation, redistribution of the circulation persists during the first three days after birth. The novelty of this study is that we were the first to study hemodynamic changes due to FGR from the prenatal period to two weeks after birth. Previous studies report on the relationship between prenatal Doppler measurements and, inter alia, neonatal cranial ultrasound and echocardiography in FGR, but not NIRS. Scherjon et al performed cranial ultrasound in FGR neonates with an interval of several hours after birth until one week postpartum. They found that fetal brain sparing is related to a higher neonatal cerebral blood flow velocity in the MCA.(9) Thus, prenatal brain sparing is associated with postnatal preferential blood flow to the brain, which is in line with our findings (Chapter 3). However, Scherjon et al only studied neonatal cerebral blood flow, whereas we investigated the relation between cerebral and systemic blood flow and overall distribution. Recently, Turan et al studied the relation between prenatal Doppler measurements in FGR and neonatal echocardiography.(10) In their study, umbilical artery (UA) PIs were not predictive of neonatal echocardiographic findings, but neonates with mild placental dysfunction did show visual evidence of impaired cardiac contractility. This may be due to the fact that no association exists. Alternatively, the changes shown by the neonatal heart are very subtle and might, therefore, not prove an association. By contrast, we did find associations between prenatal Doppler measurements and neonatal circulation, in particular redistribution of the circulation. We speculate that NIRS is a sensitive method to establish distribution of circulation in FGR in the transitional period.

**Pathophysiological process of FGR**

In case of FGR, the circulation of the fetus adapts to diminished availability of oxygen and nutrients. Baschat hypothesized about this pathophysiological process in terms of three phases; preclinical, clinical, and decompensation - the latter corresponding to fetal demise.(11) We adapted the first two phases of this hypothesis and visualized it
in a scheme in which we propose changes in growth, Doppler PI measurements, and neonatal distribution of circulation measured with NIRS (Figure 1). In the preclinical phase of FGR, a reduction in blood flow volume from the placenta occurs and, as a result, less oxygen and nutrients are available to the fetus. These metabolic changes trigger venous redistribution. More blood is diverted from the umbilical vein into the ductus venosus (DV) to the detriment of portal hepatic perfusion, resulting in reduced liver growth. Since the liver is one of the major contributors to abdominal size, the abdominal circumference no longer reaches its expected growth. At the same time, hypoxemia and hypoglycemia cause impaired myocardial contractility, as seen by decreased LAD of the fetal heart (Chapter 2). (10-12) Since our study group mostly included fetuses with normal Doppler measurements, we speculate that reduced LAD is an expression of the preclinical phase. Next, redistribution of fetal cardiac output occurs, causing increased blood flow to the brain and heart, and simultaneous peripheral vasoconstriction, i.e. abdominal organs. As a consequence, Doppler measurements start to deteriorate, resistance in the UA increases while it decreases in the MCA, CPR drops, and brain sparing is a fact. During this phase the fetus enters the clinical phase (Figure 1). (12) Apparently, this adaptation of the circulation continues until three days after birth and is reflected in lower cerebral fractional tissue oxygen extraction (FTOE) compared to renal FTOE (Chapter 3).

**Figure 1.** The pathophysiological process of fetal growth restriction (FGR).
Abbreviations: PI - pulsatility index, NIRS - near-infrared spectroscopy, FTOE - fractional tissue oxygen extraction.
Brain sparing

The association between Doppler measurements and NIRS in FGR is new. We were intrigued to find that brain sparing continued until three days after birth. Previously, Bozetti et al studied the use of NIRS in FGR, but without considering prenatal Doppler measurements, and confirmed the postnatal presence of brain sparing up to three days after birth(13) At mean 12 hours as well as mean 63 hours after birth, cerebral FTOE was lower than splanchnic FTOE in FGR infants. Unfortunately, they did not measure NIRS after 72 hours. Therefore, our finding that brain sparing had disappeared on Day 4 after birth could not be confirmed. Scherjon et al did find a significantly higher mean velocity of the MCA during the first week of postnatal life in infants with an abnormal fetal CPR compared to a normal CPR.(9) They studied infants with abnormal CPRs, but only half of them had a birth weight below the 10th percentile. We speculate that if fetuses experience brain sparing, it is associated with abnormal blood flow of the MCA for at least one week after birth. In FGR infants who experience brain sparing, however, redistribution of the entire neonatal circulation seems to adjust from four days after birth. Apparently, brain sparing itself affects neonatal cerebral blood flow longer than FGR does, whereas FGR has more influence on the distribution of circulation throughout the body.

Brain sparing not only influences postnatal circulation after FGR, it also affects the quality of general movements (GMs) one week after birth (Chapter 4). In our study, abnormal Doppler PIs of the UA and MCA, and the CPR (thus brain sparing) correlated strongly with abnormal quality of GMs on Day 7 after birth, whereas DV PIs did not. Another method to establish the infant’s wellbeing shortly after birth is the neonatal behavioral assessment scale (NBAS). Using this method, preterm and term-born FGR infants with brain sparing were studied and they were found to have abnormal scores in the motor area.(14,15) Unfortunately, these studies did not include follow-up at later ages. We reassessed GMs at three months post term and found that fidgety GMs (FM) were no longer associated with prenatal Doppler measurements. This is in line with the findings of Zuk et al who found that neurodevelopmental outcome at two years was normal in infants with normalized GMs.(16) Nevertheless, as we speculate in Chapter 4, normalization of GMs from term to three months post term might still be a risk factor for subtle brain dysfunction. Namely, at the age of one-and-a-half and two years, FGR infants with brain sparing were found to have behavioral problems more often,(17,18) and at five years they more often have lower IQs.(19) One possible explanation for impaired neurodevelopmental outcome after brain sparing is offered by Hernandez-Andrade et al. They studied regional cerebral blood perfusion at different hemodynamic stages in severe FGR and found that deterioration of the fetal condition, starting with abnormal UA and MCA PIs, was associated with a decrease in frontal brain perfusion.(20) Therefore, they suggested that an abnormal MCA PI (increased perfusion) becomes visible only
Chapter 7

after the decline of hemodynamic protection of the frontal area. Thus, brain sparing might not be a protective mechanism, but the first sign of deterioration. Conversely, in a different study, no associations were found between brain sparing and behavior at the age of eleven. (21) We speculate that once growth-restricted infants reach school age, they might, in the meantime, have compensated the poor brain perfusion experienced during the prenatal period.

Neurodevelopmental course after FGR

In Part III we present an extensive follow-up study at school age of children born small for gestational age (SGA). We referred to them as SGA and not FGR, since we had no prenatal background information such as Doppler measurements. The children participating in the study in Part III were from different cohorts than the infants in the study presented in Part II. In comparison to matched controls, in very preterm SGA children we found lower scores on performance IQ, selective attention, total motor skills, and manual dexterity (Chapter 5). Moderate preterm and full term SGA children more often had abnormal scores on attention control, and they showed a non-significant trend towards lower IQs than controls (Chapter 6). Strikingly, many neuropsychological test scores in SGA children at school age were comparable with their peers who were born appropriate for gestational age. Exceptions were attention and, only in very preterm children, performance IQ. At school age, attention was the only area affected in both preterm and term-born children born SGA. Previous studies on this topic reported conflicting results. At five to eight years, attention deficit disorder scores did not differ between preterm-born SGA children and controls, although this might be due to the use of a questionnaire rather than a standardized follow-up test. (22) At six years, being born SGA is a risk factor for attention problems, but this risk has disappeared at the age of eight. (23) Thus, attention problems seem to be present at school age in children born SGA, but apparently they disappear as children grow older. (24) We speculate that in SGA children, attention problems are present until a certain stage in a child’s cognitive development, and that these problems may disappear over time. To the best of our knowledge, it is unknown which factors contribute to this so-called catch-up phenomenon (25) of attention skills, but perhaps the severity of growth restriction, underlying placental pathology, and gender differences may exert influence. (26,27)

The percentage of children with neurodevelopmental abnormalities after FGR seems to decrease over time (Figure 2). In the FGR groups we studied, the quality of GMs on Day 7 after birth was abnormal in more than half of the infants. Subsequently, although the quality of FMs at three months post term was only abnormal in one infant, half of the infants had a quantitatively abnormal score, i.e. a motor optimality score (MOS) of less than 25. (28) At school age, we mostly found abnormal scores in cognitive functions of SGA children (follow-up in Figure 2), which is in line with the literature.
The question rises whether abnormal GMs and FMs are associated with later follow-up. Unfortunately, due to lack of time, we were unable to perform a longitudinal study in FGR including GMs and follow-up. Abnormal quality GMs in preterm non-SGA children, however, is associated with poor cognition at seven to eleven years. In addition, not only the quality of GMs, but quantitative scores of motor optimality are also associated with later neurodevelopmental outcome. Therefore, abnormal quality GMs and an abnormal MOS in the FGR group we studied in Part II, might be associated with poor cognitive outcome at school age. We already established outcome of SGA children in different cohorts (Part III), but future research is needed to assess the association between GMs and later functional outcome, specifically in FGR children. In conclusion, neuropsychological development after FGR seems to be most affected shortly after birth, yet it does have developmental consequences well into childhood. In general, functional outcome at school age after FGR is better than was previously expected.

**Figure 2.** The course of neurodevelopment after fetal growth restriction (FGR) during childhood, a cross-sectional overview. Bars show normal and abnormal percentages of the entire FGR group studied. Abnormal: GMs Day 7 poor repertoire, cramped-synchronized, or dyskinetic, FMs MOS < 25, FU mean total IQ, attention, and total motor skills of the preterm group and moderately preterm/full term groups combined. Abbreviations: GMs - general movements, FMs - fidgety movements, FU follow-up, IQ - intelligence quotient, MOS - motor optimality score.

**Early versus late FGR**

From the studies described in Parts II and III it appears that outcomes after FGR can differ between preterm and term-born infants. Table 1 summarizes the main findings of the various studies on preterm and term-born groups presented in this thesis. Increased resistance in the fetal vessels occurred approximately equally often in the preterm and term-born FGR fetuses, which we interpreted as reflecting comparable severity
Chapter 7

Table 1. The main findings of this thesis comparing preterm and term-born FGR groups.

<table>
<thead>
<tr>
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<th>Preterm</th>
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<td>Doppler PI</td>
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<td>NIRS</td>
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<td>Renal FTOE</td>
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<td>Splanchnic FTOE</td>
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<td>GMs</td>
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<tr>
<td>Day 7</td>
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<td>Association UA, MCA, CPR</td>
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<td>FMs 3 months</td>
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Follow-up

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<td>Selective attention</td>
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<td>Attention control</td>
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<td>Verbal memory: delayed recall</td>
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<td>Executive functioning</td>
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<td>Total motor score</td>
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<td>Static-dynamic balance</td>
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Doppler PI arrows represent PIs compared to clinically accepted cutoffs. NIRS arrows are FGR groups compared to each other. GMs represent whether associations with Doppler PIs were found. Follow-up arrows or “=” represent comparison with controls.

Abbreviations: PI - pulsatility index, UA - umbilical artery, MCA - middle cerebral artery, CPR - cerebroplacental ratio, DV - ductus venosus, NIRS - near-infrared spectroscopy, FTOE - fractional tissue oxygen extraction, GMs - general movements, FMs - fidgety movements, IQ - intelligence quotient.

of FGR in the two groups. Circulatory redistribution after birth was more pronounced in preterm FGR compared to term FGR (lower cerebral FTOE, and higher renal and splanchnic FTOE). Even so, fetal Doppler measurements were most strongly associated with GMs on Day 7 after birth in the term group, whereas associations with FMs did not differ between groups. In Chapter 4, we speculated that this might be due to a higher incidence of comorbidity in the preterm group. (32) Serious complications in the first days after birth may provoke abnormal GMs, and overshadow the original association between Doppler measurements and GMs. At school age, attention was affected in
both preterm and term groups, albeit in different subtests. In the very preterm group, motor function was also affected, whereas in the moderately preterm and term group this was not the case. IQ scores did not differ significantly with those of the controls in both groups, but we did see a trend towards lower scores on performance IQ in the preterm group in contrast to the term group that had lower scores, (but not statistically significant) than non-SGA controls on both total and verbal IQ.

Preterm-born FGR infants are at higher risk of perinatal morbidity and mortality than term FGR infants, especially when born before 32 weeks of gestation. In a large prospective cohort study, Bassan et al reported lower neonatal neurodevelopmental scores in preterm-born FGR infants together with increased perinatal morbidity in comparison to FGR infants born at term. In this light, our findings of more a pronounced neonatal redistribution of circulation in preterm FGR infants might be in line with these previous studies. Surprisingly, Bassan et al found no differences in neurodevelopmental outcome between preterm and term FGR infants at two and six years’ follow-up of the same cohort. This is in line with our findings at seven and eight years (Part III and Table 1), since in both groups outcomes did not differ much from those of controls – attention being the exception. We conclude that preterm-born FGR infants initially have a higher risk of complications. Once they outgrow the perinatal period, brain function no longer seems to be affected and catch-up might even have taken place. The implication might be that, in case of FGR, early delivery is considered a viable option when fetal-placental abnormalities are evident, whereas after 36 weeks of gestation non-intervention is safe.

Limitations of this thesis
The studies described in this thesis were subject to potential limitations. All studies, except the study presented in Chapter 6, were single-center studies. Therefore, the generalizability of the results needs to be established in population studies. Another consequence was that the study groups were small. Furthermore, we studied a cross section of the FGR groups: a longitudinal study of growth-restricted cases was not part of the study designs presented in this thesis. We did, however, provide an extensive overview of the consequences of FGR at different points in time, encompassing the fetal period to school age.

In this thesis we used different definitions of FGR. In Part I, we defined FGR as an EFW below the 10th percentile. Seven percent of the FGR group had abnormal PI s of the UA. In Part II, we defined FGR as an EFW or abdominal circumference below the 10th percentile, or reflecting fetal growth, and UA PI was abnormal in 60% of the cases. In Part III, we referred to the children as SGA, since no prenatal Doppler measurements were available. We defined SGA as a birth weight below the 10th percentile (Chapter 5) and below -1 standard deviation in order to increase statistical power (Chapter 6).
Therefore, the groups studied in this thesis were heterogeneous. The advantage of different definitions might be that we offer different points of view on the consequences of FGR.

**Growth charts and the detection of FGR**

A topic that we did not address in this thesis, but one that is of great importance for detecting and managing FGR, is the use of growth charts. In this thesis we used the estimated fetal weight (EFW) charts by Verburg during pregnancy, (36) and the birth weight charts by Kloosterman for neonates. (37) It is a well-known fact that true birth weight charts, such as the Kloosterman and PRN curves (the latter were developed by Stichting Perinatale Registratie, a Dutch foundation for perinatal registration) (38), are fundamentally different from EFW charts and may lead to an underestimation of the severity of growth restriction, especially in preterm infants. (39) Birth weight charts inevitably include non-healthy preterm infants with an absolute lower 10th percentile value than on a growth chart based on EFW. Preterm infants with a birth weight just above the 10th percentile according to a birth weight chart could, in fact, be FGR according to EFW growth charts. In order to identify these “hidden” FGR infants (Figure 3, space between the solid and dotted lines), some suggest using growth charts based on fetal ultrasound measurements to determine birth weight. (40) The disadvantage of this option is that EFW based on ultrasound measurements is affected by a margin of

**Figure 3.** Distribution of birth weight and estimated fetal weight. Weights are along the X-axis and the proportion of the sample along the Y-axis.

Abbreviations: SGA - small for gestational age.
±10% of the true weight, due to measurement variation. (40) When it comes to the study presented in Part III, in which we used birth weight curves to define SGA, we have to keep in mind that we might have missed the “hidden” SGA cases. In Chapter 6, however, we defined SGA as a birth weight of -1 standard deviation or more, thus below the 16th percentile. Therefore, in this chapter, we might already have included the “hidden” SGA children. It is important to realize that accurate knowledge of the duration of pregnancy is essential to assess the adequacy of fetal growth and to determine whether a fetus is growth-restricted.

Conclusions and implications
This thesis provides insight into the developmental course of infants who experienced growth restriction in utero. We found that in FGR, offline assessment of LAD using STIC could improve conventional online M-mode, so as to detect subtle differences in fetal cardiac dysfunction. Therefore, this method may be useful to detect, prenatally, those FGR infants at risk of cardiovascular problems, who might benefit from postnatal interventions to improve their future cardiovascular health. Next, in the development from fetus to newborn infant, fetal brain sparing was associated with neonatal redistribution of circulation and with neurological functioning one week after birth. Since cardiovascular instability may be caused by myocardial dysfunction, the effects of persistent fetal circulation might become important in modifying early neonatal management. (10) Medical caregivers, such as neonatologists, general pediatricians, and nurses should be aware of the consequences of fetal brain sparing in infants born after FGR.

At school age, differences in functional outcome were small between children who experienced growth restriction in utero and controls. Attention was the exception. It was impaired in both preterm and term-born children. In addition, total and fine motor skills were poorer in preterm SGA children than in matched preterm non-SGA controls. Even though abnormal neuropsychological outcomes after FGR seem to decrease as children grow older, attention problems should not be dismissed. Especially parents and teachers, who experience these children in everyday life, should be aware of these potential deficits due to FGR.

In the studies presented here, long-term neuropsychological consequences of FGR seem moderate. This does, however, not imply that consequences of FGR in other areas should be neglected. We emphasize the effect that small birth size might have on the cardiovascular system. FGR induces, for example, primary cardiac and vascular changes at five years, (42) which might be related to an increased risk of ischemic heart disease in later life. (43)
Future perspectives

For future studies we suggest examining whether associations between prenatal Doppler measurements and neonatal circulation and neurology can be confirmed in larger samples. Furthermore, associations between prenatal Doppler measurements and neonatal circulation and neurology might become clearer if study groups were defined by Doppler abnormalities. Not only studies on perinatal consequences of growth restriction, but also long-term neuropsychological research would benefit from ultrasound data being included. Since Doppler measurements have, nowadays, entered the standard management protocol of FGR, soon these parameters should be made accessible for long-term follow-up. We also urgently recommend that the 48 infants studied in Part II are followed up until school age in order to assess whether GMs are associated with late functional outcome in growth-restricted children. Finally, we recommend a multidisciplinary approach to FGR, both in clinical management and research.
References


