Chapter 1

General Introduction And Outline Of The Thesis

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Introduction

Associations of intrauterine growth restriction and pregnancy outcomes.

Pregnancies complicated by intrauterine growth restriction (IUGR) and children born small-for-gestational-age (SGA) are known to have higher perinatal morbidity and mortality, even at term.[1] Perinatal morbidity includes meconium aspiration, asphyxia, hypothermia and hypoglycaemia.[2] In addition, neuro-cognitive development and intelligence quotient have been correlated to weight at birth, as well as cerebral palsy.[3-6] On the long term in later life, low birth weight has been associated with cardiac ischemic disease in adults, and other chronic conditions such as diabetes and hypertension. Moreover, low birth weight is designated as one of the "big four" determinants in perinatal mortality in the Netherlands; 85% of perinatal deaths are associated with one of these "big four": congenital abnormality, premature birth (<37 weeks gestation), low birth weight (<P10) and low Apgar score (<7).[7;8]

Impaired fetal growth has a complex ethiology, where genetics, placental insufficiency, maternal and fetal conditions and environmental factors interact. Low birth weight is correlated with socio-demographic risk factors (i.e. non-marital status and lower education levels), smoking, congenital malformations, intrauterine infections and maternal diseases. Several of these factors can be modified to a certain degree, preferably before conception. It is known that cessation of smoking, even during pregnancy can positively influence birth weight.[9-10-11-12] Preconception programmes focus on BMI and smoking as they have major impact on IUGR and stillbirth.[13]

Definitions and discrimination of IUGR and SGA

Differentiating between SGA and IUGR during pregnancy is very difficult. The focus first of all is on detecting small babies and once detected focus on fetal condition and growth potential.

The terms intrauterine growth restriction (IUGR) and small-for-gestational-age

(SGA) have been used interchangeably, creating confusion on the topic. Intrauterine growth retardation implies that intrauterine growth has been inhibited and that the fetus has not attained its optimal growth potential (fetal growth restriction). IUGR is a clinical term, but the diagnosis is usually based in retrospect on small size for gestational age at birth. The American Society of Obstetricians and Gynaecologists defines fetal growth restriction as an estimated weight below the 10th percentile (P) for gestational age.[14] SGA children have an actual birth weight below the 10th percentile and seem to represent both physiologically and constitutionally small children. Some say that in this group only 30% is growth restricted.[15-17]

Roth et al. tried to differentiate between IUGR and SGA by calculating standard deviation scores (SDS) of AC and estimated fetal weight (EFW). Growth was expressed as change in SDS in time (Δ AC and Δ EFW). A Δ AC of -1.5 was the best predictor of growth restriction. IUGR was defined as Δ AC between first and last ultrasound greater than -1.5 (SDS) and SGA when Δ AC was less than -1.5 SDS. Despite increased fetal surveillance, nearly one-third of the term IUGR as well as SGA fetuses had suffered some, albeit minor, neurological impairment (e.g. passive tone, cortical thumbs, and hypotonia) at birth compared to a control group with normal growth. They concluded that the pattern of growth in the third trimester does not affect outcome at 1 year, therefore their differentiation between IUGR and SGA was not found helpful on the long term.[18]

Another possibility to classify fetal growth has been to relate abdominal circumference with head circumference.[19] If these measurements are symmetrical fetal growth is considered to be normal. Dashe et al. compared asymmetrically and symmetrically SGA infants to appropriate for gestational age (AGA) matched babies and found that symmetric SGA infants were not at increased risk of morbidity compared with AGA infants. A neonatal outcome composite, including one or more of respiratory distress, intraventricular haemorrhage, sepsis, or neonatal death, was more frequent among asymmetric SGA than AGA infants. Symmetric SGA infants were not at increased risk of morbidity compared with AGA infants.

Thus screening for asymmetric SGA seems helpful to detect children at risk for adverse outcome.[20]

The 10th percentile of birth weight for gestational age is associated with an increased but variable risk of neonatal death.[21] Regardless of placental function, EFW by ultrasound below the 3rd percentile discriminates SGA fetuses with higher risk of adverse perinatal outcome from SGA children with outcomes similar to normally grown fetuses, defined as a birth weight greater than the 10th percentile.[22-23]
At 26 weeks of gestation, infants at the 10th percentile experience a 3-fold risk of dying within the first 28 days of life (relative to a group with a 45th to 55th percentile group); whereas at 40 weeks, the risk is 1.13.23 Smaller babies in general have worse outcomes as is illustrated by Seeds; already below the 15th percentile the risk of fetal death is two-fold.[24]

In a prospective 26 years follow-up study of 14189 children, of whom 1064 were born small-for-gestational-age (<5th percentile), adults born SGA had significant differences in academic achievement and professional attainment compared with adults who were appropriate for gestational age (AGA). There were no long-term social or emotional consequences of being SGA: these adults were as likely to be employed, married, and satisfied with life.[25]

To dwell on the numerous different calculations for EFW based on ultrasound measurements lies beyond the scope of this thesis, but again emphasises the complexities that have to be handled in IUGR. [26-28]

In summary, many suggestions have been done to distinguish genuine IUGR from SGA. Considering that IUGR and SGA are not synonym there is an obvious strong correlation between the two entities. To realise a clear differentiation between these entities seems to be one of the main goals of prenatal care. Nevertheless, all children that are suspected to be too small before birth potentially have an increased risk for adverse outcome. At present, they need more attention regardless

of the definition used. We can only prospectively improve perinatal outcomes with increased surveillance and possible treatments.

Screening

Accuracy and importance of screening for SGA and IUGR

Throughout the intrauterine period we are challenged to determine the fetal condition. Of major importance in this challenge is the estimation of the fetal weight. Unfortunately we have discovered repeatedly that we are performing very meagre in predicting the exact neonatal weight at birth.

Most studies report sensitivities as low as 25% to 32% to detect SGA.[29-31] In an urban teaching hospital in Wisconsin they failed to detect 90% of children with a birth weight below 10th percentile.[32]

While some have illustrated that detection of a small fetus mainly increases obstetrical interventions without improving neonatal outcome[30;31;33,] others affirm the importance of antenatal detection of SGA fetus to improve their outcome. [34;35] Frøen et al. found that many stillborn babies were small-for-gestational-age. They concluded that it was unlikely to be a constitutional smallness, but represented a preponderance of intrauterine growth restriction.[36] They calculated individualised growth standards in stillbirths that were classified unexplained. With these individually adjusted fetal weight standards, 51% of unexplained stillbirths were too small. They plead that many ante partum stillbirths, currently designated as unexplained, may be avoidable if slow fetal growth could be recognised as a warning sign. In a recent Dutch study term stillbirths were prospectively collected and audited by an expert panel. During a 2 year study period within a specific region, 37735 normally formed infants were delivered ≥ 37 weeks of gestation. There were 60 stillbirths (1.59 per 1,000, 95%CI 1.19-1.99). Most of these stillbirths occurred during apparently uncomplicated pregnancies. Twenty-one infants (35%) were small-for-gestational age but growth restriction was only suspected in 10 (47.6%) of these cases.[37]

Improvement of screening and surveillance of IUGR.

Once detected clinicians are challenged to distinguish intrauterine growth restriction from "just" constitutionally small children.

A history of IUGR is associated with recurrence of IUGR and a higher incidence of stillbirth in a subsequent pregnancy. Therefore medical history can help to screen for IUGR.[38;39]

Whereas evidence for the use of serial funding height measurement (SFH) alone, as a screening tool was indecisive[40], plotting SFH measurement on customised charts is also found to be a useful screening tool in detection of IUGR.41 This tool gives a significantly higher antenatal detection rate of small for gestational age babies compared to routine antenatal care (48% v 29%, odds ratio 2.2, 95% confidence interval 1.1 to 4.5). It gave a slight decrease in repeat (two or more) third trimester scans (OR 0.8, CI 0.6-1.0, P = 0.08) and fewer admissions to the antenatal ward (OR 0.6, CI 0.4-0.7, P < 0.001). However, there were no differences in perinatal outcome.

Customised standards for fetal growth and birth weight improve the detection of IUGR by better distinction between physiological and pathological smallness and have led to internationally applicable norms. [42-44] Individualising fetal growth potential is the basis of these customised standards.

These standards are calculated by adjusting for fetal sex and maternal characteristics as weight, parity and ethnic origin. The fetal growth potential is predicted after exclusion of smoking, hypertension, diabetes and previous preterm delivery. Finally, the optimal weight is projected backwards for all gestational points, using an ultrasound growth based proportionality curve. Computer software calculate the individually adjusted curves.[45]

Development of these customised growth curves has been propagated widely.

Some studies challenge this method and found that the process of customising population weight-for-gestational-age standards to account for maternal characteristics does little to improve prediction of perinatal mortality.[46-47] In a Dutch study comparing conventional growth curves and the customised Gardosi curves the P50 and P10 showed great overlap between 34 and 38 weeks gestation and therefore customised growth curves would be of no additional help in the prediction of perinatal morbidity at term.[48] In the Netherlands these customised curves are not applied in standard obstetrical management.
Another feature in IUGR screening and surveillance is measurement of amniotic fluid volume. Although the amniotic fluid index (AFI) is one of the first variables to decrease[49], more than 90% of patients with IUGR or SGA have an AFI above 5.0 cm.[50] Oligohydramnios with IUGR seems to be a poor predictor of peripartum complications.[51] Studies aiming to improve the estimation of AFI by comparing AFI, largest amniotic fluid pocket dimension or a more subjective approach did not show much improvement in the use of this variable for the prediction of perinatal morbidity.[52-53] Decreased fetal movements are associated with IUGR and stillbirth, however there is insufficient and contradicting evidence for the use of this parameter on pregnancy outcomes.[54-56]

Significant reductions of perinatal mortality and adverse outcomes can be realised by using Doppler of the umbilical artery (UA), however only in high-risk pregnancies (e.g. where IUGR was suspected, maternal hypertension, previous pregnancy loss).[57] Doppler flow measurement has become the cornerstone in screening for IUGR and assessment of placental function in IUGR.[58] Abnormal Doppler patterns in IUGR are characterised by absent or reversed end-diastolic velocities in the umbilical artery (UA) and have been found important predictors for perinatal morbidity and mortality in severe early onset IUGR (<32-34 weeks gestation) and can be present weeks before acute deterioration. It is concluded that delivery should be considered if ductus venosus Doppler or short-term variation becomes persistently abnormal.49 Other longitudinal studies also on deteriorating of early-onset IUGR described that the pulsatility index (PI) in the middle cerebral artery (MCA) pro-

gressively becomes abnormal. In the time sequence of changes in fetal monitoring variables in early-onset IUGR amniotic fluid index and umbilical artery pulsatility index were the first variables to become abnormal, followed by the MCA, aorta, short-term variation, ductus venosus and inferior vena cava. [59-61] The concept of fetal brain-sparing illustrated by changes in cerebral artery Doppler has been studied by Scherjon et al. They linked increased umbilical-cerebral Doppler ratio (UCR) to abnormal cognitive function in early onset IUGR. At 5 years of age, children with brain-sparing had a 9 point lower IQ compared to children with normal UCR.[62]

In term IUGR umbilical artery (UA) Doppler recordings seem to be differently related to pathofysiology, and absent or reversed end-diastolic velocities are less prominent. In a cohort of 282 early term SGA children 2-year cognitive development was related to a number of significant perinatal factors, including the UA Doppler. However, in 15% of these SGA babies a suboptimal neurodevelopment was found albeit normal UA Doppler indices.[63]

Observational studies show that in term growth restriction decreased MCA-PI could be a proxy for adverse neonatal outcome, independently of UA-PI.[64] Eixarch compared children with IUGR beyond 37 weeks gestation to AGA children by the Ages and Stages Questionnaire (ASQ) at two years of age. Brain-sparing (decreased MCA-PI) was associated with a higher rate of acidosis at birth. Children with brain-sparing scored lower in communication, problem-solving and personal-social areas, whereas children with normal MCA-PI did not differ from AGA children.[65] Presence of redistribution by detection of abnormal cerebral blood flows in the middle cerebral artery has recently been found to identify small fetus at term with normal umbilical artery Doppler waveforms with an increased risk of fetal distress and delivery by caesarean section.[66] Without these flow abnormalities the occurrence of fetal distress seems to be minimal; only 4% fetal distress requiring a caesarean section.[67] There are no randomised trials for timing of delivery in term growth restricted babies with the use of MCA Doppler.

Management

Determining the optimal management strategy for delivery in IUGR

The next important and crucial question is, assuming we have detected a pregnancy complicated by IUGR as accurately as possible, what would be the appropriate management strategy to improve neonatal and obstetrical outcomes.
From very early in gestation, the fetus appears to be sensitive to the nutrient status. One of the most immediate responses to a decrease in substrate delivery is a reduction in fetal growth, which appears to be the most important factor in balancing reduced oxygen delivery and consumption. Placental insufficiency can result in reduction of nutrient supply (e.g. oxygen, glucose, amino acids and fatty acids). Cordocentesis studies in humans have shown that small-for-gestational-age fetuses are relatively hypercapnic, hypoxic, hyperlacticaemic, acidotic and hypoglycaemic compared with appropriate-for-gestational-age fetuses.[68]

The fetus responds with hemodynamic and metabolic compensations, favouring organs such as the heart, adrenals and brain (brain-sparing). Although short-term survival may be guaranteed by these adaptations, there may be a long-term cost (e.g. cognitive dysfunction, chronic lung disease and necrotizing enterocolitis).[69] In animal models, growth restriction can also lead to functional deficits and affect behaviour and brain composition, with more prolonged periods of hypoxia being associated with a worse outcome.[70-71] As a result of chronic oxygen and nutrient deprivation in sheep reduced myelination of subcortical white matter, a reduction in the number of Purkinje neurons in the cerebellum and severe cortical astrocytosis have been described, as well as damage to the hippocampus.[72]

In these situations if the fetus is clearly deteriorating and suggested to be severely hypoxic or acidaemic showed by CTG changes the clinicians will end the pregnancy and start delivery. In all other situations the management options are expectant management or induction of labour.
Continuing pregnancy in an undernourished environment will likely result in impairment of fetal growth and this will impose detrimental effects on fetal devel-

opment or even result in intrauterine death. These arguments would plead for induction of labour to pre-empt possible stillbirth and neonatal morbidity and mortality.

On the other hand the fetus could fare better by further growing and maturing even in a possible undernourished environment. In addition induced prematurity by induction of labour, even beyond 36 weeks gestation might cause perinatal morbidity due to (iatrogenic) prematurity, an additional argument for expectant management.[73-77] Therefore postponing delivery with an expectant management policy could be the appropriate strategy to improve neonatal outcome.
Another possible rationale to postpone delivery is to await spontaneous onset of labour and prevent an increase in the rate of instrumental deliveries and caesarean sections associated with induction of labour .[78-79] Though many recent intervention studies for other indications actually show a reduction of artificial deliveries in induced delivery groups.[80-82]

Most evidence on timing of delivery and management policies in IUGR is from retrospective studies looking at cohorts of children born with a birth weight below the 10th percentile or from pregnancies at lower gestational ages.[83-86] Prospective studies how to ensure safe fetal monitoring in pregnancy where delivery is deferred, have actually not been performed in the term period; these studies are urgently needed to be able to evaluate effects of currently used and newer scheme's for fetal surveillance regimens in e.g. impaired fetal growth.[87]

McCowan et al. compared two regimens of fetal surveillance for small-for-gestational-age fetuses with normal results of umbilical artery Doppler velocimetry. In this study fetuses with normal results of umbilical artery Doppler velocimetric studies had low rates of neonatal morbidity regardless of whether antenatal surveillance was undertaken at planned fortnightly or planned twice-weekly intervals. Intervention (induction of labour) was less common in the fortnightly surveillance group. This study was performed in the preterm period and the study did not have

the power to detect clinically important differences in neonatal outcomes or in caesarean delivery rates.[88]

Results of the Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) study have not been published yet.[89] The hypothesis of this study is that among preterm growth-restricted infants, timing delivery based on the fetal ductus venosus increases the rate of normal infant neurological outcome compared with timing of delivery based on severe changes in fetal heart short-term variation. The TRUFFLE study did not include term gestations.

The Growth Restriction Intervention Trial (GRIT) study approached questions about timing of delivery of the growth restricted fetus also in the preterm period (< 34 weeks gestation).[90] They compared the effect of early delivery to pre-empt terminal hypoxaemia with delaying for as long as possible to increase maturity. They found with expectant management a gestational age increase of on average 4 days. Total deaths (ante partum and neonatal death combined) prior to discharge were comparable between the immediate delivery group and the delay group. Delaying delivery caused some stillbirths, but immediate delivery resulted in an almost exactly equal number of perinatal deaths. However, the rate of caesarean section was three times higher in the immediate delivery group. The GRIT found little difference neither in overall mortality nor in 2, 6 and 13-year outcomes of children.[91-92] Early intervention does not seem to improve short-, nor long term outcomes.

Aim of the thesis - DIGITAT study

Until recently there was no consensus on the appropriate policy in IUGR in the term period. A digital questionnaire sent to Dutch gynaecologists and residents showed wide divergence in assumptions about IUGR at term, and reflects the equipoise in management of IUGR in the Netherlands.[93] (Figures 1-3).

To establish consensus and to collect evidence on the best management policy in IUGR at term, the DIGITAT-trial (Disproportionate Intrauterine Growth Intervention Trial At Term) was designed. Initially a small randomised pilot study was performed

to compare induction of labour with an expectant monitoring management in suspected IUGR at term in 33 women. It showed feasibility to accomplish a larger multi-centre trial with sufficient power.[94] Embedded in the structure of the Dutch Obstetrical Consortium [95] more than 50 hospitals, academic and non-academic, agreed to participate in this multi-centre randomised controlled trial to enrol 650 pregnant women suspected of IUGR. The aim of the DIGITAT study was to compare the effect of induction of labour with an expectant management monitoring mother and child for suspected intrauterine growth restriction at term in singleton pregnancies in cephalic presentation beyond 36 weeks gestation on neonatal and obstetrical outcomes.[96] The results of the DIGITAT study including the randomised trial form the basis of this thesis and will be described and discussed.

Figure 1
Estimated risk of stillbirth after expectant management with an EFW of 2000 grams at 40 weeks gestational age. Data from an inquire under Dutch gynaecologists and residents in March 2008

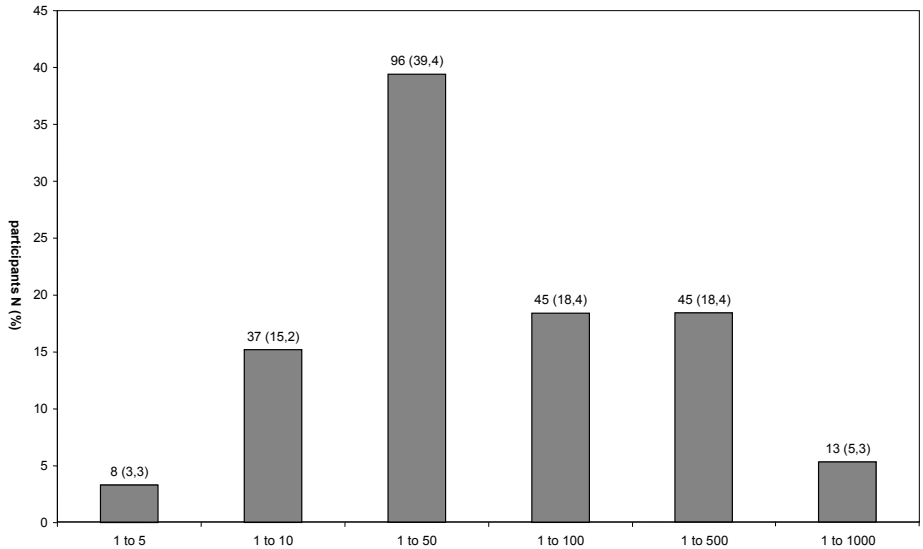


Figure 2
The estimated effect of induction of labour on neonatal morbidity. Data from an inquire under Dutch gynaecologists and residents in March 2008

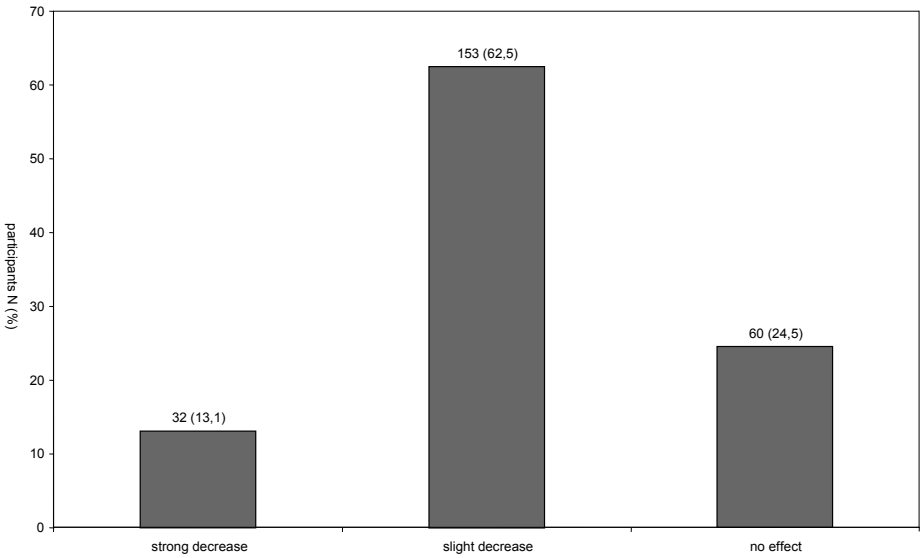
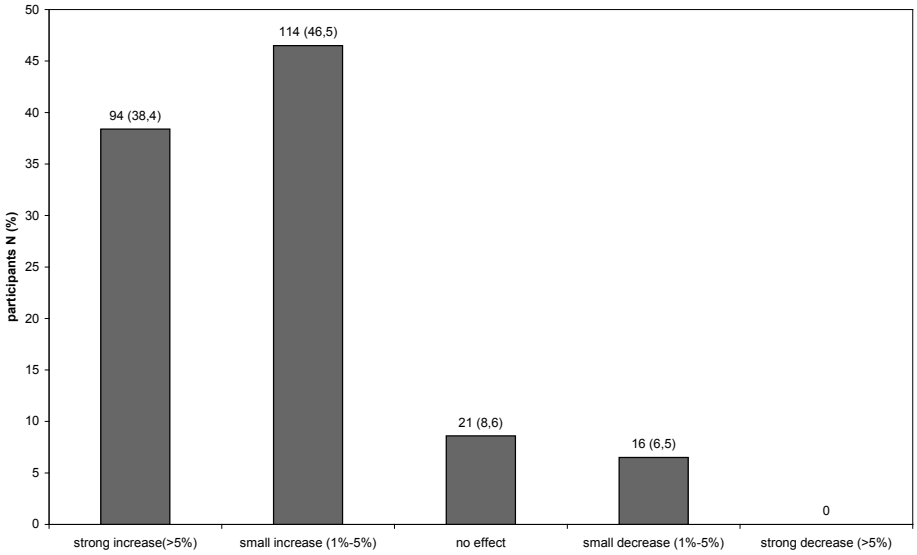


Figure 3
The assumed effect of induction of labour on the rate of caesarean section. Data from an inquire under Dutch gynaecologists and residents in March 2008



Outline of the thesis

Chapter 2 describes the influence of induction of labour on neonatal outcomes immediately after birth and mode of delivery in a retrospective cohort of children born with a birth weight below the 10th percentile. These data were derived from a national dataset (LVR-2).

Chapter 3 outlines the trial protocol and the aims of the DIGITAT study. It reflects on existing information on intrauterine growth restriction and describes the primary and secondary analyses that were carried out.

Chapter 4 contains the primary outcomes of the trial, adverse neonatal outcomes and route of delivery after induction or expectant management in at term IUGR. Maternal outcomes are also compared between the two strategies.

Chapter 5 displays a secondary analysis that approached neonatal outcomes in more detail. For this analysis we assessed the (morbidity assessment index in newborns) MAIN-score.

Chapter 6 handles about results of non-participants, but who consented to the use of their medical data. To examine external validity of the trial we compared their data that were collected in the same prospective way, to data of trial-participants.

Chapter 7 contains the maternal health-related quality of life (HR-QoL) after induction or expectant management in IUGR at term.

Chapter 8 describes the economic analysis and cost-effectiveness of both induction and expectant monitoring that was performed alongside the trial.

Chapter 9 presents long-term follow up of children who were delivered during

the trial. The effects on (neuro)developmental and behavioural outcome at 2 years of age of induced labour compared with expectant management in intrauterine growth restricted infants are described.

Chapter 10 displays data of a comparison between labour induction and expectant management through integration of trial outcomes and patients preferences.

Chapter 11 gives a different perspective on at term IUGR by describing a study looking at outcomes of pregnancies where diagnosis of IUGR was missed, compared to pregnancies where IUGR was diagnosed.

Chapter 12 discusses the strategies in IUGR at term by evaluation the trial results, secondary analysis and retrospective studies.

Chapter 13
Summary

Chapter 14
Nederlandse samenvatting

Appendices
Authors and collaborators on the DIGITAT-trial
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Publications
Curriculum Vitae

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