Strategies in Intrauterine Growth Restriction At Term

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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

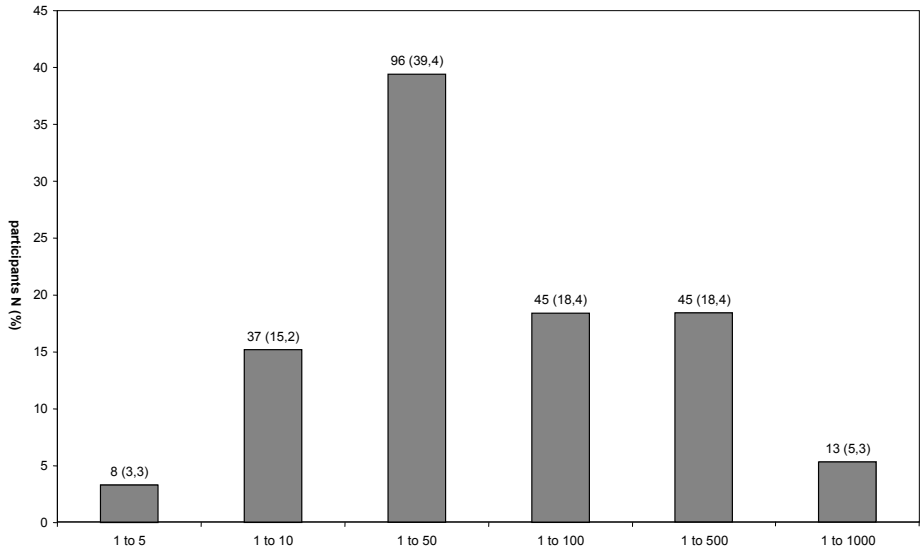


Figure 2
The estimated effect of induction of labour on neonatal morbidity. Data from an inquire under Dutch gynaecologists and residents in March 2008

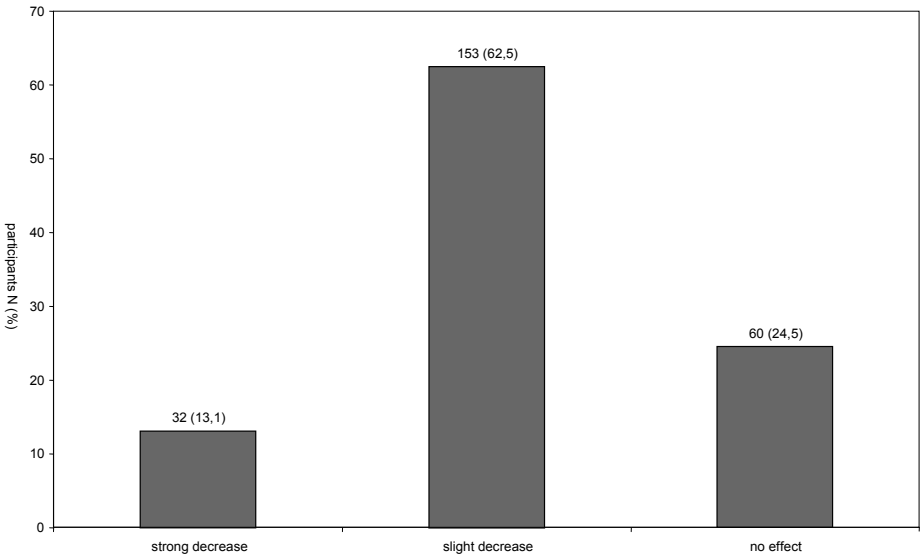
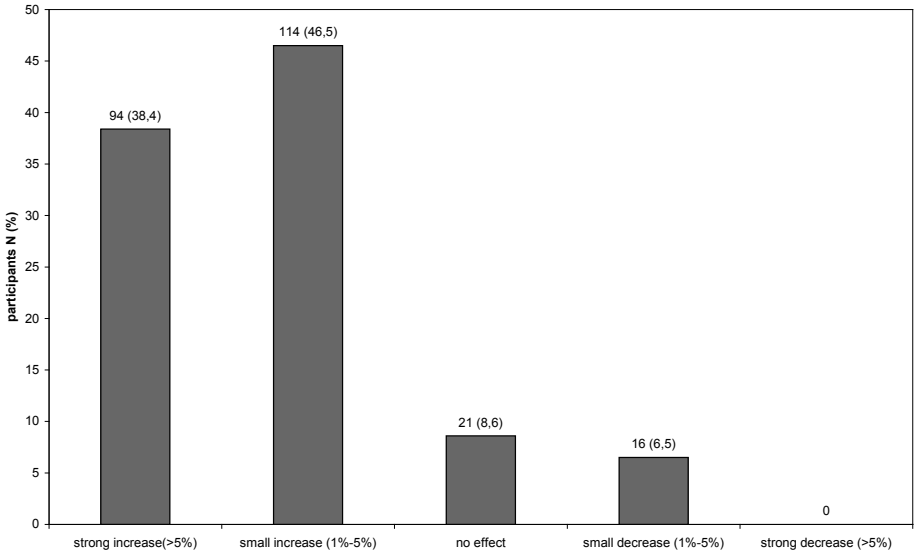


Figure 3
The assumed effect of induction of labour on the rate of caesarean section. Data from an inquire under Dutch gynaecologists and residents in March 2008



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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Chapter 2

Labour and Neonatal Outcome in Small for Gestational Age Babies Delivered Beyond 36+0 Weeks: A Retrospective Cohort Study

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Abstract

Objective : Small for gestational age (SGA) is associated with increased neonatal morbidity and mortality. At present, evidence on whether these pregnancies should be managed expectantly or by induction is lacking. To get insight in current policy we analysed data of the National Dutch Perinatal Registry (PRN).

Methods: We used data of all nulliparae between 2000 and 2005 with a singleton in cephalic presentation beyond 36+0 weeks, with a birth weight below the 10th percentile. We analysed two groups of pregnancies: (I) with isolated SGA and (II) with both SGA and hypertensive disorders. Onset of labour was related to route of delivery and neonatal outcome.

Results: Induction was associated with a higher risk of emergency caesarean section (CS), without improvement in neonatal outcome. For women with isolated SGA the relative risk of emergency CS after induction was 2.3 (95% Confidence Interval [CI] 2.1 to 2.5) and for women with both SGA and hypertensive disorders the relative risk was 2.7 (95% CI 2.3 to 3.1).

Conclusions: Induction in pregnancies complicated by SGA at term is associated with a higher risk of instrumental deliveries without improvement of neonatal outcome. Prospective studies are needed to determine the best strategy in suspected IUGR at term.

Introduction

Intrauterine growth restriction (IUGR) and hypertensive disorders in pregnancy are important complications of pregnancy and are, also in term pregnancies, associated with an increased risk of maternal and perinatal morbidity and mortality[1–5]. At present there is evidence on the optimal treatment of pregnancies complicated by hypertension at term concerning the prevention of maternal morbidity [6]. However, evidence on the best management strategy for at term intrauterine growth restriction concerning neonatal outcome and labour process is still lacking. Dutch guidelines on the subject suggest either expectant management under strict monitoring of mother and child or induction of labour. On the one hand induction might preempt intrauterine fetal death. On the other hand induction of labour is thought to be associated with an increased rate of instrumental deliveries or emergency caesarean sections in retrospective studies[7–9]. Also neonatal outcome might be less favourable, related to induction of labour at a relatively early gestational age [10–12]. On the contrary, it has been demonstrated prospectively that induction of labour does not increase the risk for caesarean section while it reduces the risk of severe maternal morbidity [6]. Composite neonatal outcome in this study showed comparable neonatal outcome after induction and an expectant monitoring policy, but these children were not explicitly growth restricted [6]. To compare the neonatal outcome and intervention rates between induction and expectant monitoring of pregnancies complicated by growth restriction at term a multicentre randomised trial, the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT trial), was performed [13]. Prior to the results of this trial, we investigated current management policy on this subject in The Netherlands and analysed retrospectively data of the National Dutch Perinatal Registry (PRN) of pregnancies complicated by SGA at term to examine the onset of labour related to the mode of delivery and immediate neonatal outcome.

Methods

In the National Dutch Perinatal Registry (PRN) a distinction is made between primary care by midwives of low-risk pregnancies (LVR1) and secondary and tertiary care by obstetricians for women with an increased perinatal risk (LVR2). We used data of the LVR2 between 2000 and 2005 to select those children delivered with a birth weight below the 10th percentile. In addition, we registered if these pregnancies were complicated by preeclampsia or gestational hypertension. Only nulliparae with a singleton pregnancy in cephalic presentation that ended after 36+0 weeks were included. We excluded women with pregnancies complicated by stillbirths as well as women who delivered a child with congenital abnormalities. Gestational hypertension was defined as diastolic blood pressure above 90 mmHg (Korotkoff V), measured at two occasions in normotensive women before pregnancy. Preeclampsia was defined as a diastolic blood pressure above 90 mmHg and proteinuria of at least 300 milligrams per 24 hours [14]. SGA was defined as a birth weight below the 10th percentile, according to the Dutch growth charts of Kloosterman [15]. Between January first 2000 and December 31st 2004 a total of 253.235 nulliparae with a singleton pregnancy delivered after 36+0 weeks under secondary and tertiary care. Of these 253.235 pregnancies 799 neonates died before delivery. Of the remaining 252.436 two groups of women were analysed: (i) 14.416 women who delivered a child with a birth weight below the 10th percentile without hypertension and (ii) 4574 women with pregnancies complicated by both IUGR and hypertensive disorders. Of all these women the onset of labour was recorded this was either a spontaneous onset, induction of labour with prostaglandins or amniotomy, or an elective caesarean section. In both groups of women onset of labour was related to the labour process (spontaneously, instrumental vaginal delivery and emergency or elective caesarean section) and to immediate neonatal outcome (intrapartum death, live birth with Apgar score <7 versus Apgar score ≥7 after 5 minutes). Adverse neonatal outcome was defined by neonatal outcome of 5-minute Apgar score <7 or intrapartum death. Both labour process and adverse neonatal outcome were primary outcomes of this retrospective study. Differences in the groups between the labour process and outcome were expressed as relative risks with confidence intervals of 95%. Statistical analysis was performed using SPSS software (version 16.0, Chicago, IL).

Results

A total of 14.416 normotensive women delivered a child with a birth weight below the 10th percentile (group I). Table 1 shows the data of 14.294 women of whom both onset of labour and outcome of delivery, was known. Out of 14.347 pregnancies the immediate neonatal outcome as well as onset of labour was known (Table 2).

Table 1
Process of labour in pregnancies complicated by SGA.

	Route of delivery				RR (95% CI)	
Onset of labour	**Spontaneous vaginal**	**Instrumental delivery**	**Emergency caesarean**	**Elective caesarean**	**Emergency caesarean**	**Instrumental delivery**
Amniotomy 231 (2)	151	43	37	0	1.3 (0.95–1.7)	0.87 (0.73–1.0)
Oxytocine 1235 (9)	778	221	236	0	1.5 (1.3–1.7)	0.93 (0.86–1.0)
Prostaglandins 2191 (15)	1176	394	621	0	2.3 (2.1–2.5)	1.16 (1.1–1.2)
Spontaneous onset 10182 (71)	6125	2780	1277	0	ref	ref
Planned caesarean 455 (3)	0	0	0	455	n.a.	n.a.
Total 14.294/14.416	8230	3438	2171	455		

Displayed n (%). RR: relative risk; 95% CI: 95% confidence interval; ref: reference; n.a.: not appropriate

Table 2
Neonatal condition after birth in pregnancies complicated by SGA.

	Neonatal outcome			RR (95% CI)
	Intrapartum death	**AS < 7**	**AS ≥ 7**	**AS < 7 or Intrapartum death**
Amniotomy	0	7 (3.0)	224 (97.0)	0.96 (0.46–2.0)
Oxytocine	3 (0.2)	31 (2.5)	1202 (97.3)	0.88 (0.62–1.2)
Prostaglandins	5 (0.2)	53 (2.4)	2131 (97.4)	0.84 (0.64–1.1)
Spontaneous onset	30 (0.2)	291 (2.8)	9891 (97.0)	Ref
Planned caesarean	1 (0.2)	21 (4.4)	457 (95.4)	1.5 (0.96–2.2)
Total n= 14.347/14.416	39	403	13.905	

Displayed n (%). AS: Apgar-score after 5 minutes, RR: relative risk; 95% CI: 95% confidence interval; ref: reference; n.a.: not appropriate

Out of 4.574 women with pregnancies complicated by hypertensive disorders (preeclampsia or gestational hypertension) a child with a birth weight below the 10th percentile was born (group II). Table 3 shows the results of the 4540 women of whom the onset of labour as well as route of delivery was known.
Table 4 displays the results of 4557 women of whom both onset of labour and immediate neonatal outcome were known.

Table 3
Process of labour in pregnancies complicated by SGA and hypertensive disorders (with or without proteinuria).

	Route of delivery				RR (95% CI)	
Onset of labour	**Spontaneous vaginal**	**Instrumental delivery**	**Emergency caesarean**	**Elective caesarean**	**Emergency caesarean**	**Instrumental delivery**
Amniotomy 112 (3)	63	26	23	0	1.6 (1.1–2.3)	1.1 (0.91–1.4)
Oxytocine 720 (16)	420	148	152	0	1.6 (1.3 – 1.9)	1.1 (0.97–1.2)
Prostaglandins 1733 (39)	872	280	621	0	2.7 (2.3–3.1)	1.3 (1.2–1.4)
Spontaneous onset 1558 (34)	959	394	205	0	ref	ref
Planned caesarean 377 (8)	0	0	0	377	n.a.	n.a.
Total 4540/4574	2314	848	1001	377		

Displayed n (%). RR: relative risk; 95% CI: 95% confidence interval; ref: reference; n.a.: not appropriate

Table 4
Neonatal condition after birth in pregnancies complicated by SGA and hypertensive disorders (with or without proteinuria).

	Neonatal outcome			RR (95% CI)
	Intrapartum death	**AS < 7**	**AS ≥ 7**	**AS < 7 or Intrapartum death**
Amniotomy	0	4 (4.0)	108 (96.0)	1.4 (0.50–3.7)
Oxytocine	0	23 (3.0)	697 (97.0)	1.2 (0.74–2.0)
Prostaglandins	2 (0.1)	42 (2.4)	1726 (97.5)	0.95 (0.62–1.4)
Spontaneous onset	1 (0.1)	40 (2.5)	1519 (97.4)	Ref
Planned caesarean	1 (0.2)	19 (4.8)	374 (95.0)	1.9 (1.1–3.2)
Total 4557/4574	4	128	4424	

Displayed n (%). AS: Apgar score after 5 minutes, RR: relative risk; 95% CI: 95% confidence interval; ref: reference; n.a.: not appropriate

In both SGA groups, we found a higher risk of instrumental delivery after induction of labour with prostaglandins (Tables 1 and 3). We also found a higher risk of emergency caesarean section after induction of labour with oxytocine or amniotomy, but this was most obvious after priming with prostaglandins; in group I with isolated SGA the relative risk for emergency caesarean section was 2.3 (95% confidence interval (CI) 2.1 to 2.5) and in group II (IUGR complicated by preeclampsia or gestational hypertension) the relative risk for emergency caesarean was 2.7 (95% CI 2.3 to 3.1). Induction of labour with prostaglandines was not associated with an increased risk of adverse neonatal outcome.
For the women with a combination of SGA and hypertensive disorders we found a higher risk of adverse neonatal outcome after elective caesarean section (RR 1.9; 95% CI 1.1 to 3.2).

Discussion

We examined a cohort of 18.990 women who delivered a child that was small for gestational age in the presence or absence of hypertensive disorders at term. In this cohort we found a distinct association between induction of labour and a higher risk of emergency caesarean sections. This association was most obvious in priming with prostaglandins. We also found a higher risk of instrumental deliveries after induction of labour, whereas induction did not improve the composed adverse neonatal outcome (5-minute Apgar score <7 and intrapartum death).The strength of the present study is that analysis was performed on a large cohort of women who delivered a child with a birth weight below the 10th percentile. We did not find a benefit of inducing labour for isolated SGA nor for SGA with pregnancy-related hypertensive disorders for the immediate neonatal outcome. In pregnancies with a suspected growth restricted child, there are still doubts concerning the best policy [16]. Inducing labour might prevent possible perinatal morbidity and mortality, by freeing the growth restricted child from the undernourished environment. On the contrary observational studies showed that antenatal detection of growth restriction may be associated with an increased incidence of obstetric interventions, with no demonstrable positive effect upon the short-term neonatal outcome [17]. Also higher rates of preterm delivery are found mainly as a consequence of medical interventions to avoid fetal compromise in children with an antenatal diagnosis of intrauterine growth retardation [18].

Like other retrospective studies, we found that induction of labour in pregnancies, complicated by both SGA and hypertensive disorders in pregnancy, is associated with an increase in the caesarean section rate. In a study on induction of labour in primigravid women a doubling in the numbers of caesarean sections was found related to induction. This outcome was independent of the reason of induction [7]. This finding has to be weighted against the risk for complications for both mother and child in a next pregnancy [19]. However, most studies contain retrospective data, and there is evidence to doubt that these findings also apply in prospective trials [6]. Unfortunately, we can not exclude a possible selection bias, where the most severe cases (i.e., with the worse antenatal assessments) being induced with a less favourable cervix, as information on maternal and fetal condition as well as cervical condition are not registered in the PRN database. Moreover, one can only speculate about outcomes if these pregnancies would not have been induced but spontaneous onset of labour was awaited.

In our cohort we selected children retrospectively after they were born with a birth weight below the 10th percentile, so actually we selected children that were born small for gestational age. We cannot therefore automatically translate the results of this study to pregnancies in which IUGR is suspected antenatally by ultrasound. We were also not informed on ethnicity, which could be an important explaining variable for the different outcomes. It is well known that the use of customised growth curves results in a better selection of children who are actually growth restricted and in a better risk selection of perinatal mortality and morbidity [20]. In The Netherlands these curves are not generally applied and the PRN does not contain all items for the calculation of these customised curves retrospectively.

In both groups of women direct neonatal outcome after elective caesarean section was remarkably less optimal than after a delivery that started vaginally. Fetal compromise after elective caesarean before 39 weeks of gestation might have been a contributing factor for that finding [21]. Furthermore, the occurrence of maternal hypotension due to spinal anaesthesia, leading to hypoperfusion of the placenta in an already compromised fetal condition, could be an explaining factor [22]. Moreover, we cannot exclude that elective caesarean section was performed in the most

compromised pregnancies (e.g., with nonreassuring fetal heart rate) and subsequently represent a worse adverse outcome.

In a pilot study on pregnancies with IUGR at term it was found that it is feasible to randomise for this complication between immediate induction of labour or to a careful waiting policy until spontaneous delivery[23]. The study showed a randomisation to delivery interval of two weeks and an increase in mean birth weight of 100 grams in the expectant management group. No differences in obstetrical interventions and neonatal morbidity were found. This study was underpowered for neonatal outcome, and evidence on the best management strategy awaits prospective evaluation. The DIGITAT trial (Disproportionate Intrauterine Growth Intervention Trial At Term, ISRCT10363217) is investigating early induction versus expectant management in pregnancies complicated by IUGR at term, and results are underway [13]. The trial randomised 650 women and studied similar policies as the HYPITAT trial did for hypertension during pregnancy [6]. These trials are embedded in the Dutch Obstetric Consortium. Over 50 hospitals, academic and nonacademic, participated in these two trials (http://www.studies-obsgyn.nl).

In conclusion, data collected via the National Dutch Perinatal Registry show that induction of labour is associated with an increased risk of emergency caesarean section and instrumental deliveries in pregnancies that delivered a child with a birth weight below the 10th percentile with or without preeclampsia or gestational hypertension at term. The risk on instrumental delivery is particularly high when labour is induced with prostaglandins. Compared to spontaneous delivery, induction of labour does not seem to improve the neonatal outcomes immediately after birth. However, these retrospective data represent outcomes in children selected after they are born with a low birth weight and should not be extrapolated to settings where growth restriction is suspected antenatally.

Results of the DIGITAT trial, concerning not only medical outcomes but also cost, quality of life, and treatment preference analyses, as well as data of long-term neo-

natal followup will help to elucidate aspects of the best management strategy in IUGR at term.

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Chapter 3

Disproportionate Intrauterine Growth Intervention Trial At Term: DIGITAT-the protocol.

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BMC Pregnancy Childbirth. 2007 Jul 10;7:12.

Abstract

Background: Around 80% of intrauterine growth restricted (IUGR) infants are born at term. They have an increase in perinatal mortality and morbidity including behavioral problems, minor developmental delay and spastic cerebral palsy. Management is controversial, in particular the decision whether to induce labour or await spontaneous delivery with strict fetal and maternal surveillance. We propose a randomised trial to compare effectiveness, costs and maternal quality of life for induction of labour versus expectant management in women with a suspected IUGR fetus at term.

Methods/Design: The proposed trial is a multi-centre randomised study in pregnant women who are suspected on clinical grounds of having an IUGR child at a gestational age between 36+0 and 41+0 weeks. After informed consent women will be randomly allocated to either induction of labour or expectant management with maternal and fetal monitoring. Randomisation will be web-based. The primary outcome measure will be a composite neonatal morbidity and mortality. Secondary outcomes will be severe maternal morbidity, maternal quality of life and costs. Moreover, we aim to assess (neuro)developmental and neurobehavioral outcome at two years as assessed by a postal enquiry (Child Behavioral Check List-CBCL and Ages and Stages Questionnaire-ASQ). Analysis will be by intention to treat. Quality of life analysis and a preference study will also be performed in the same study population. Health technology assessment with an economic analysis is part of this so called DIGITAT trial (Disproportionate Intrauterine Growth Intervention Trial At Term). The study aims to include 325 patients per arm.

Discussion: This trial will provide evidence for which strategy is superior in terms of neonatal and maternal morbidity and mortality, costs and maternal quality of life aspects. This will be the first randomised trial for IUGR at term.

Background

Around 80% of intrauterine growth restricted (IUGR) infants are born at term.[1] When pregnancy is complicated by IUGR, there is, whether term or preterm, a clear association with an increase in neonatal mortality and neonatal morbidity (short and long term). [2-4] The long term morbidity ranges from behavioral problems and minor developmental delay to spastic cerebral palsy. [5-10] However, not all studies, especially after excluding congenital anomalies, confirm these findings.[11] Besides fetal asphyxia, meconium aspiration, fetal heart rate abnormalities and low Apgar score, also more admittances to and longer stays at neonatal intensive care units are reported. This might partly be related to a higher prevalence of hypoglycaemia, neonatal sepsis, hypothermia and haematological problems as thrombocytopenia and polycythemia in these neonates.[12-14]

When a fetus is small for gestational age (SGA), defined on the basis of a birth weight below the 10th centile, there is the concern that the fetus might be afflicted by IUGR.[15] As SGA is defined on the basis of an arbitrary chosen cutoff birth weight centile, not all infants falling below the 10th centile are abnormally small because of growth restriction. Many neonates with a birth weight below the 10th centile are representing the normal spectrum of fetal growth.[11] Variation in birth weight is related to many factors as maternal height, weight, parity and fetal gender, but also ethnicity.16 For that reason optimal growth for any fetus should be related to the fetus' own individual optimal growth curve.[17-19] Intrauterine growth restriction has to be defined on further knowledge such as Doppler abnormalities as seen in placental perfusion, eventually in combination with abnormalities in cerebral perfusion [20;21] and possibly also by neonatal measurements as the Ponderal Index.[22;23]

A reduction of fetal growth is exponentially associated with a higher perinatal mortality [24] and morbidity.[25-26] Doppler umbilical artery studies have shown that absence of end diastolic velocities, indicative of IUGR based on severe placental insufficiency is associated with a higher rate of caesarean deliveries and an increased

incidence of perinatal and neonatal mortality. [27-30] However, a normal umbilical artery Doppler study at term gestation might be falsely reassuring, while a normal cerebral artery study might identify the fetus not likely having a major adverse outcome.[31]

Most of the growth restricted children experience an accelerated growth, especially of the head circumference, during the first 6 months after birth.[32] However, this upward centile crossing or 'catch up growth' is not complete, even at the age of seven years.33 Moreover head circumference seems to correlate with cognitive outcome.[34]
Long-term neurological and cognitive development of the IUGR infant at term have been studied extensively. The Ponderal Index among IUGR infants, but also among infants with a normal birth weight, is an independent predictor of neonatal morbidity: the lower the Ponderal Index the higher morbidity.[25] Learning difficulties, defects in speech and mild neurological deficits and behavioral problems have been reported to occur more in term neonates born SGA.[35-36] At school ages (7-8 years) temperamental differences and differences in play behavior are apparent[37], most probably contributing to increased rate of school failure found in IUGR infants.

Long-term morbidity might be resulting from subtle nutritional insults to the brain in utero. Although the brain growth spurt, being the most vulnerable period of the human brain, spans a broad period between mid pregnancy and 6 months of postnatal age[38;39], it is shown that growth failure occurring around term shows a strong association with cognitive disturbances as a poorer mental and psychomotor development at two years of age.[40] However, not all studies, even at preschool age show this trend of increased problems in growth restricted infants.[41-42] Besides (neuro)developmental consequences it is now also clear that children who were undernourished during pregnancy (e.g. born with a birth weight more than 2 SD below the mean birth weight) and especially in combination having had a compensatory growth trajectory during childhood have an increased risk in later

life for diabetes, hypertension and cardiovascular diseases.[43]

Given the data from studies concerning the effect of under-nutrition on the brain and the effects on long-term cognitive and behavioral outcome, evaluation of the possible clinical benefit of early induction of delivery, pre-empting a detrimental effect of chronic under nutrition on the fetal brain intervention, is important. By such an intervention it might be possible to start earlier with a more optimal feeding, compensating for the poor intra-uterine environment. Induction of labor is very often common practice in cases of suspected IUGR.[44-45] In the Netherlands at 33 up to 36 weeks of gestation, 63% of IUGR pregnancies were induced, whereas from 37 weeks onwards this percentage is 23%; more than double the percentage in non-IUGR pregnancies. In a Dutch obstetric cohort of 14.294 primigravid women with IUGR pregnancies, 29% of these pregnancies were induced.[46] In these pregnancies complicated by IUGR, induction of labour was associated with an increased risk of instrumental deliveries and emergency caesarean section, but no difference in neonatal outcome immediately after birth was found.

At present, there is no uniformity on the management of women with IUGR at term. Although there is no doubt that the intra-uterine growth retarded fetus should be considered as high risk, and should be monitored, there is no consensus on which diagnostic methods to evaluate fetal condition and subsequent intervention is best. It is unclear whether in this situation either induction of labour or expectant management is beneficial for the mother and her baby, since evidence on the subject is lacking.
For preterm pregnancies complicated by intra-uterine growth retardation, an international randomised clinical trial recently showed that expectant management had little benefit over early delivery with respect to short term neonatal outcome.[47] However, results of this trial cannot be extrapolated to the situation at term.

The lack of consensus on the subject in the Netherlands is demonstrated by the fact that in 2002 in women with a SGA child, labour was induced in 32% of these

women, whereas labour started spontaneously in 56% of these women, the remaining 11% had an elective caesarean section. These data are based on actual birth weight, and the clinical situation is even more complicated by the fact that the antenatal diagnosis of a SGA child is often difficult to make and easily missed in clinical practice.
In view of this clinical dilemma, we propose a randomised clinical trial in which induction of labour is compared with expectant monitoring in women with a suspected IUGR child at term. We will compare maternal outcome, neonatal outcome and maternal quality of life, as well as costs. Moreover, we will collect, in both randomisation arms, data of the diagnostic tests used in fetal surveillance, i.e. fetal heart rate pattern, sonographic measurement of the amniotic fluid index and Doppler measurement of the umbilical artery and the fetal medial cerebral artery in women.

Methods/Design

Aims

The aim of this study is to investigate whether induction of labour or expectant management is the best strategy in terms of neonatal and maternal morbidity and mortality, costs and maternal quality of life aspect in pregnancies complicated by IUGR from 36 weeks gestational weeks onwards.

Study Design and Setting

We will perform a randomised controlled multi centre study.This trial is embedded in the Dutch Obstetric Consortium, a collaboration of obstetric hospitals in the Netherlands. Approximately 40 hospitals, including all 10 university hospitals, teaching hospitals and district hospitals will participate in this trial.

Participants/Eligibility criteria

All women with a singleton pregnancy, with a child in cephalic presentation, with suspicion of IUGR (Fetal Abdominal Circumference < 10th centile, Estimated Fetal Weight < 10th percentile as defined by local protocols), or decreased relative growth though still > 10th centile, e.g. from 70th centile to 40th centile) are eligible. Gestational age should be between 36+0 weeks and 41+0 weeks. Women with a history of caesarean section, serious congenital defects, ruptured membranes, renal diseases, diabetes mellitus, or positive HIV serology will be excluded.

Procedures, recruitment, randomisation and collection of baseline data

All women with a singleton pregnancy who present at one of the participating clinics will be referred to an obstetrician or a specifically appointed research nurse/midwife for counselling. Eligible women receive participant information. After written consent, they are randomised by means of a web-based application. Stratification will be applied for previous vaginal birth (nullipara versus multipara) and for centre. Randomisation will be in a 1:1 ratio for induction of labour or expectant management.

Patients that withhold consent for randomisation are asked permission for data collection on pregnancy outcome. Participation to the quality of life study and long-term follow up (Child Behavioural Check Lists-CBCL and Ages and Stages Questionnaire-ASQ) is asked separately.

Baseline demographic, past obstetric and medical histories will be recorded for all women. Cervical length will be measured at the time of randomisation. The quality of life questionnaires are filled out before randomization, after randomization, 6 weeks postpartum and 6 months postpartum. The questionnaires contain the Hospital Anxiety and Depression Scale (HADS), EuroQoL 5D3L, Short Form (SF-36), Symptom Check List (SCL-90), and questions on background characteristics, intervention preparedness, risk perception and experience with the current pregnancy.

Intervention

When randomised to the induction arm, induction of labor must start within 48 hours after randomisation. Induction of labor can be proceded according to local protocol (among other things cervical ripening with prostaglandin-gel or tablets or with amniotomy, with or without the use of oxytocin). When allocated to the expectant management group patients will not be induced unless the fetal or maternal condition deteriorates and this is for the attending obstetrician a reason for induction. The patients will be observed, e.g. with fetal and maternal monitoring according to local practice, until labour starts spontaneously. However, monitoring must at least include measurement of the umbilical artery Doppler waveform, fetal heart rate tracing, blood pressure and urine analysis for albuminuria weekly. Doppler studies of the medial cerebral artery are optional. Reasons for interventions and time interval between randomisation and labour will be collected.

Follow up of women and infants

All details of delivery, maternal and fetal assessments and admittance during pregnancy are recorded in the case record form that is accessible at the website. In case of admittance of the child to the neonatal intensive care unit, details of this admittance are also recorded.

Long-term follow up of children will be done by recording growth after birth as measured at the local infant follow up clinics.

Outcome measures

The primary outcome measure will be a bad composite neonatal outcome. Adverse neonatal outcome will be defined as death before hospital discharge, a 5-minute Apgar score < 7, an umbilical artery pH < 7.05 or admission to the neonatal intensive care. Secondary outcome measures are mode of delivery and time until delivery, length of admittance at the neonatal intensive care, maternal morbidity, hospitalisation of the mother for fetal and maternal surveillance, quality of life, and costs. In the present proposal, no funding is asked for long term follow-up of the child, yet. However, if additional funding can be obtained children's behavioural-,

and (neuro)development will assessed by administering with a postal enquiry the Child Behaviour Checklist-CBCL and Ages and Stages Questionnaire- ASQ by their parents after 2 years.

Statistical issues

Sample size calculations

The study is designed as an equivalence study, whereby both treatments will have the same incidence of the primary outcome measure of combined bad neonatal outcome. This incidence is assumed to be 6%[46]. The null hypothesis is that both treatments will not be equivalent. To detect equivalence with a power of 80% a sample size in both groups of 325 will be needed (PASS SOFTWARE). The margin of equivalence, given in terms of the difference, extends from -5.5 % to +5.5 %. The actual difference is 0 %. The calculations assume that two, one-sided Z tests are used. The significance level of the test is 0.05.

Data analysis

Data will initially be analysed according to the intention to treat method. The main outcome variable, 'bad neonatal outcome', will be assessed by calculating rates in the two groups, relative risks and 95% confidence intervals as well as numbers needed to treat.

Time to delivery will be evaluated by Kaplan-Meier estimates, with account for differing durations of gestation at entry, and will be tested with the log rank test. The other secondary outcome measures will be approached similarly to the primary outcome measure. The analysis will be stratified for parity and centre.

Non response and inclusion bias

As non-response for follow up is overrepresented in certain outcome-related risk categories such as in non-native mothers, mothers with lower educational level and in mothers with boys, statistical methods that use imputation of missing data

have to be applied.[48] To prevent inclusion bias all patients who were asked but decline randomisation, will be asked for permission to collect data on pregnancy outcome and further follow up according to the same schedule as the randomised patients.

Economic evaluation

The aim of the economic evaluation is to compare optimality, in terms of costs and health effects, of both strategies. As the clinical study is based on equivalence design we hypothesize that there will be no relevant difference between maternal and neonatal outcome in the two strategies. The economic evaluation will be in the form of a cost-effectiveness analysis (CEA), in which the optimal strategy is defined as the strategy with the largest health gain at the smallest costs.

Ethical considerations

This study has been approved by the ethics committee of the Leiden University Medical Centre (Ref. No. P04.210).

Discussion

There is uncertainty about the management of IUGR at term, whether to leave the child in utero until spontaneous labour starts, or to prevent undernutrition by prolonged pregnancy in a poor intra-uterine environment by inducing labour. This latter treatment modality will most probably be at the cost of an increase in instrumental deliveries.46 As optimal management of a pregnancy at term suspected to be complicated by IUGR remains unclear, it is a challenge to develop criteria for inducing delivery. An increase in fetal surveillance in these pregnancies (with normal umbilical artery studies) is thought to be associated with more inductions of labour and a shortening of gestational age.[49] Neonatal morbidity (and mortality) is low in term SGA neonates3, nevertheless these neonates cannot be considered just "healthy small babies".

Although our primary aim is to study pregnancies complicated by IUGR, the in-

clusion criteria are obviously based on a suspicion of a SGA child, as we include women with a fetus with a Fetal Abdominal Circumference < 10th centile or an Estimated Fetal Weight < 10th centile. By patient's characteristics, such as ethnicity, maternal and paternal length as well as tests results as the amount of amniotic fluid or the Doppler of the arteria umblicalis, we will be able to evaluate which pregnancies are at risk for a poor neonatal outcome.

In summary, at the present, there is controversy as to which strategy is the best when IUGR at term is suspected. Whether to induce labour or to await spontaneous labour under strict fetal and maternal monitoring remains debatable because of a lack of evidence. Patients' management partly depends on the attending doctor and on local protocols. To resolve these issues, we will compare both strategies in the multi centre randomised trial – DIGITAT. In a pilot study carried out in one of the participating hospitals, we examined the feasibility of the DIGITAT-trial. Preliminary data from this small pilot show that the interval between randomisation and labour was 2 weeks shorter and birth-weight was 100 grams less in the pregnancies that were directly terminated by induction.[50]

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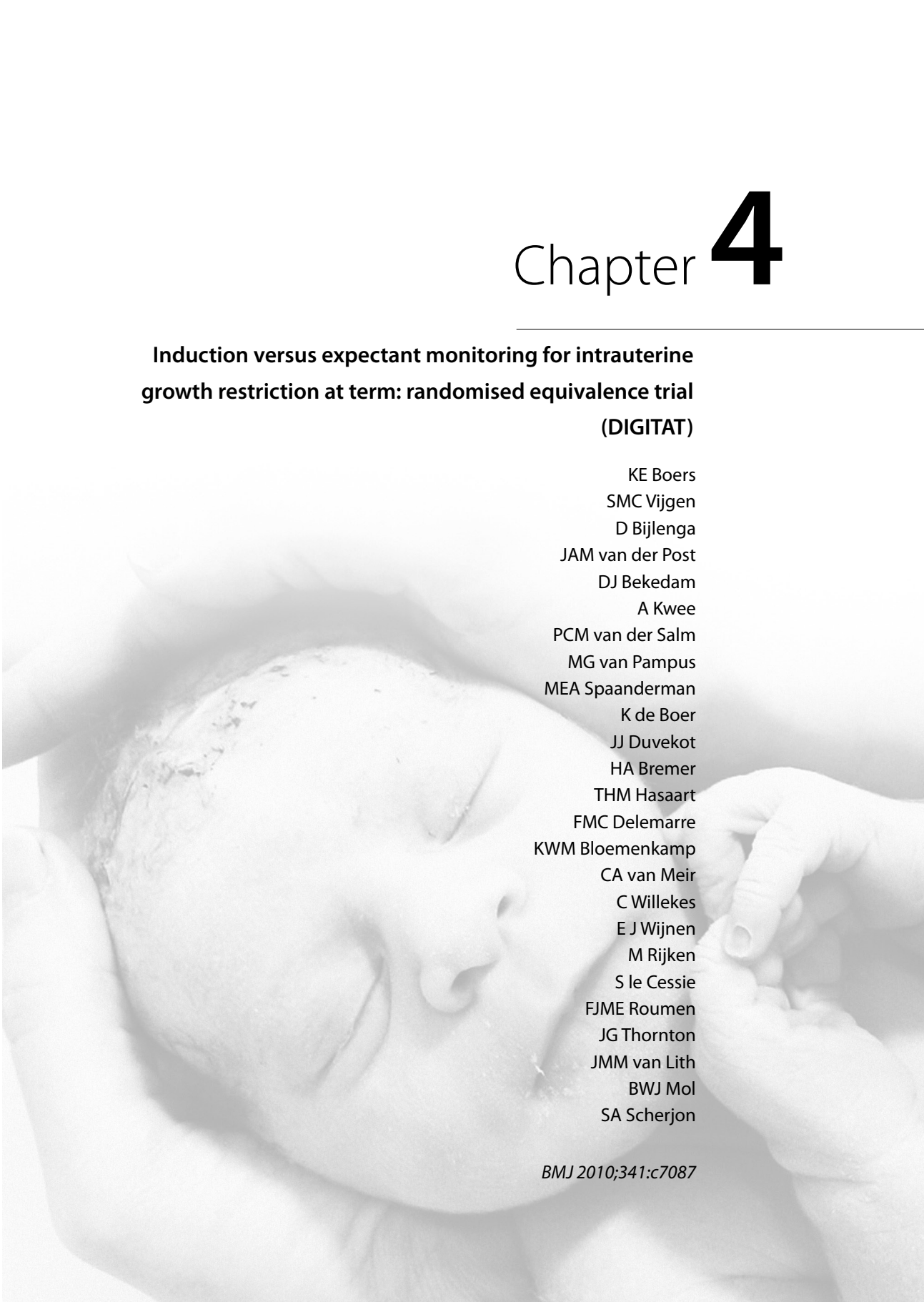
Chapter 4

Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT)

KE Boers
SMC Vijgen
D Bijlenga
JAM van der Post
DJ Bekedam
A Kwee
PCM van der Salm
MG van Pampus
MEA Spaanderman
K de Boer
JJ Duvekot
HA Bremer
THM Hasaart
FMC Delemarre
KWM Bloemenkamp
CA van Meir
C Willekes
E J Wijnen
M Rijken
S le Cessie
FJME Roumen
JG Thornton
JMM van Lith
BWJ Mol
SA Scherjon

BMJ 2010;341:c7087



Abstract

Objective: To compare the effect of induction of labour with a policy of expectant monitoring for intrauterine growth restriction near term.

Design: Multicentre randomised equivalence trial (the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT)).
Setting Eight academic and 44 non-academic hospitals in the Netherlands between November 2004 and November 2008.
Participants Pregnant women who had a singleton pregnancy beyond 36+0 weeks gestation with suspected intrauterine growth restriction.
Interventions Induction of labour or expectant monitoring.

Main outcome measures : The primary outcome was a composite measure of adverse neonatal outcome, defined as death before hospital discharge, five minute Apgar score of less than 7, umbilical artery pH of less than 7.05, or admission to the intensive care unit. Operative delivery (vaginal instrumental delivery or caesarean section) was a secondary outcome. Analysis was by intention to treat, with confidence intervals calculated for the differences in percentages or means.

Results: 321 pregnant women were randomly allocated to induction and 329 to expectant monitoring. Induction group infants were delivered 10 days earlier (mean difference -9.9 days, 95% CI -11.3 to -8.6) and weighed 130 g less (mean difference -130 g, 95% CI -188 g to -71 g) than babies born to women in the expectant monitoring group. A total of 17 (5.3%) infants in the induction group experienced the composite adverse neonatal outcome, compared with 20 (6·1%) in the expectant monitoring group (difference -0.8%, 95% CI -4.3% to 3.2%). Caesarean sections were performed on 45 (14.0%) mothers in the induction group and 45 (13.7%) in the expectant monitoring group (difference 0.3%, 95% CI -5.0% to 5.6%).

Conclusions: In women with suspected intrauterine growth restriction at term, we

found no important differences in adverse outcomes between induction of labour and expectant monitoring. Patients who are keen on non-intervention can safely choose expectant management with intensive maternal and fetal monitoring; however, it is rational to choose induction to prevent possible neonatal morbidity and stillbirth.
Trial registration International Standard Randomised Controlled Trial number ISRCTN10363217.

Introduction

Most infants with intrauterine growth restriction are born at term.[1] Growth restriction so late in gestation is associated with increased perinatal morbidity in the form of fetal distress, hypoglycaemia, seizures, behavioural problems, cerebral palsy, and cardiovascular disease, as well as perinatal mortality.[2-11] Obstetricians often induce labour in cases of intrauterine growth restriction for fear of neonatal morbidity and later stillbirth. However, observational comparisons of such infants with matched fetuses delivered after spontaneous labour have shown no reduction in short term adverse neonatal outcomes. Induction might increase obstetric intervention[12-14] and even cause neonatal morbidity if performed before 39 weeks.[15-18] For these reasons, expectant management with maternal and fetal monitoring is a commonly followed strategy.
The Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT) was designed to compare the effect of induction of labour with expectant monitoring on a composite adverse neonatal outcome and on operative delivery rates in infants with suspected growth restriction beyond 36 weeks' gestation. In a pilot trial comparing these two interventions in 33 women, neonatal outcomes and operative delivery rates were comparable, but the precision of the estimate of the effect size was limited.[19]

Methods

The trial was run by the Dutch Obstetric Consortium, a collaboration of perinatal centres in the Netherlands, and approved by the University of Leiden institutional review board. The study was staffed by obstetricians, research nurses, and midwives associated with the Dutch Obstetric Consortium. They counselled and recruited participants, monitored compliance with allocated treatment protocols, and collected outcome data.

Recruitment ran from November 2004 to November 2008. The study began in four hospitals, but by the end of the study period recruitment had been rolled out to 52 maternity hospitals in Holland. Making the crude assumptions that the average centre recruited for half the trial duration of three years (that is,18 months), that each centre delivered 1500 women a year (adjusting for women seen only in labour or who were ineligible because of multiple pregnancy or breech pregnancy), and assuming that half of all growth restricted fetuses are detectable, we anticipated that about 1326 potentially eligible women would be identified over the recruitment period.

Participants

Pregnant women between 36+0 and 41+0 weeks' gestation who had a singleton fetus in cephalic presentation, suspected intrauterine growth restriction, and who were under specialised obstetric care were recruited. Suspected intrauterine growth restriction was defined as fetal abdominal circumference below the 10th percentile, estimated fetal weight below the 10th percentile, flattening of the growth curve in the third trimester (as judged by a clinician), or all the presence of all three factors.[20] Both fetuses with abnormal Doppler flow velocity measurements and those with normal Doppler flow velocity measurements were included.

The DIGITAT recruitment period overlapped with recruitment for the Hypertension Intervention Trial At Term (HYPITAT),[22] which compared similar interventions in women with gestational hypertension and mild pre-eclampsia at term. Patients with both suspected intrauterine growth restriction and hypertension were preferentially recruited to DIGITAT, and women could not participate in both studies. Gestational hypertension and pre-eclampsia were defined according to criteria

from the International Society for the Study of Hypertension in Pregnancy.[23] Oligohydramnios was defined as an amniotic fluid index of 5 cm or less.
Exclusion criteria were previous caesarean section, diabetes mellitus or gestational diabetes requiring insulin therapy, renal failure, HIV seropositivity, prelabour rupture of membranes, severe pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count), or a fetus with aneuploidy or congenital abnormalities suspected on ultrasound. Fetuses with decreased or absent movements, and those with abnormal heart rate tracings, were also excluded.
Cervical length was measured using transvaginal sonography and vaginal digital examination was performed to assess the Bishop score before randomisation.[21]

Randomisation

Participant data were entered into a secure web based database. Women were randomly allocated to either induction or expectant monitoring in a 1:1 ratio using varied sized block randomisation with stratification for centre and parity (nulliparous or parous women). Women who declined consent for randomisation but authorised use of their medical data were treated at the discretion of the local obstetrician and included in the database. These data were used to study external validity of the trial. Women who refused both randomisation and collection of identifiable data were registered anonymously. It was not possible to blind participants, obstetricians, or outcome assessors. Written informed consent was obtained from all participants before randomisation.
Participants allocated to the induction of labour group were induced within 48 hours of randomisation. If the Bishop score at randomisation was greater than 6, labour was induced with amniotomy and, if necessary, augmented with oxytocin. Otherwise cervical ripening was performed with intracervical or intravaginal prostaglandin (E1 or E2 analogue, repeated once after six hours) or a Foley balloon catheter filled with 30 mL sodium chloride.[24]
Participants allocated to the expectant monitoring group were monitored until the onset of spontaneous labour with daily fetal movement counts and twice weekly heart rate tracings, ultrasound examination, maternal blood pressure measurement, assessment of proteinuria, laboratory tests of liver and kidney function, and full blood count. Women were monitored as either an outpatient or an inpatient,

according to local protocol. In the expectant monitoring group, induction of labour or planned caesarean section was performed for obstetrical indications—such as suboptimal fetal heart rate tracings, prolonged rupture of membranes, or postmaturity between T+7 and T+14 days—at the obstetrician's discretion.

Outcomes

The primary outcome was a composite measure of adverse neonatal outcome. This was defined as death before hospital discharge, five minute Apgar score of less than 7, umbilical artery pH of less than 7·05, or admission to neonatal intensive care. If the umbilical artery pH data were missing and all other components of the composite outcome were normal, the neonatal outcome was classified as normal. Secondary outcomes were delivery by caesarean section, instrumental vaginal delivery, length of stay in the neonatal intensive care or neonatal ward, length of stay in the maternal hospital, and maternal morbidity. The latter was defined as post-partum haemorrhage of more than 1000 mL, development of gestational hypertension or pre-eclampsia (according to International Society for the Study of Hypertension in Pregnancy criteria),[22] eclampsia, pulmonary oedema, thromboembolism, or any other serious adverse event.

Study design, sample size, and statistical analysis

The trial was designed as an equivalence trial in which the null hypothesis was that the difference in the risk of the composite outcome between the two treatment groups was greater than 5.5% (absolute percentage). Assuming that the rate in the control group was 6% (on the basis of data from the National Dutch Perinatal Registry[25], this meant that we would exclude the null hypothesis and conclude that the two treatments were equivalent if the boundaries of the confidence interval of the observed risk difference were between -5.5% and 5.5%. With a 0.05 risk of type I error (α) and 80% (1-β) power, we calculated that we would require 650 participants (325 per group). The sample size formula for equivalence testing on page 39 of Jones et al [26] was used to calculate these numbers, assuming that the induction rate and the control rate were both equal to 6% under the alternative of equivalence.

Data were analysed according to the intention to treat principle. Continuous vari-

ables were summarised as means with standard deviations, or medians with interquartile ranges (IQR). Treatment effects were presented as differences in means or percentages with 95% confidence intervals (CI). Equivalence of the primary outcome measure was tested by checking if the 95% CI of the risk difference lay within the equivalence margins. Continuous variables were compared using the Student's t test or the non-parametric Mann-Whitney U test. The $\chi 2$ square test was used for categorical variables. Instances were more than 5% of the observations were missing are indicated in the footnotes of the tables.

In a secondary analysis, the primary and secondary outcomes for the two groups were compared after exclusion of women with hypertension related diseases (pre-existent hypertension, gestational hypertension, and pre-eclampsia) at randomisation. Given that randomisation was stratified for centre and parity, we also performed a stratified analysis for the primary outcome by using logistic regression with parity as fixed covariate and centre as random covariate. Statistical analyses were performed using SPSS software (version 16.0; IBM, Chicago, IL) and Stata software (version 10.1; Stata Corp, College Station, TX).

Results

A total of 1116 potentially eligible women were identified. Of these women, 14 refused any use of identifiable data and 452 declined randomisation. This left 650 participants, who were randomly assigned to induction (n=321) or expectant monitoring (n=329) (figure 1). The baseline characteristics of participants in the two randomised arms and in the non-randomised group are shown in table 1.

Figuur 1
Flow diagram of the process of the trial

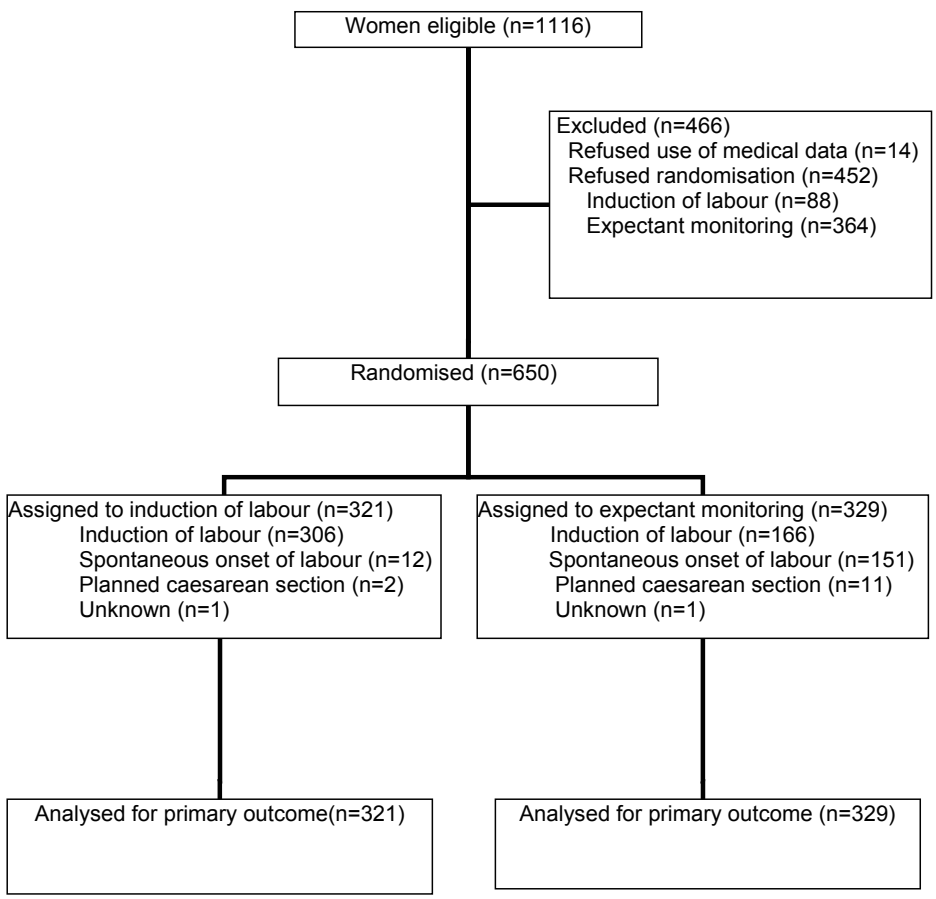


Table 1
Demographic and baseline characteristics of randomised and non randomised participants

Characteristic	Induction of labour group (n=321)	Expectant monitoring group (n=329)	Non-randomised group (n=452)
Nulliparous	182 (56·7)	201 (61·1)	275 (61·0)
Maternal age	27 (23 - 31)	27 (23 - 31)	31 (27 - 34)
BMI at study entry†	22 (20 - 25)	22 (20 - 26)	21 (20 - 24)
Gestational age (days)	263 (258-269)	263 (258-270)	262 (258-269)
Caucasian‡	254 (83·6)	253 (81·1)	344(83·3)
Education			
Lower professional school	168 (52·3)	170 (51·7)	149 (33·0)
Medium professional school	26 (8·1)	37 (11·2)	93 (20·6)
Unknown	127 (39·6)	122 (37·1)	209 (46·3)
Maternal smoking§	138 (46·9)	127 (40·8)	114 (26·9)
Blood pressure at booking			
Systolic	115(105 - 120)	114 (106 - 120)	115 (110 - 120)
Diastolic	70 (60 - 75)	66 (60 - 75)	70 (60 - 75)
Women with gestational hypertension	9 (2·8)	19 (5·8)	25 (5·5)
Women with pre-eclampsia	18 (5·6)	27 (8·2)	27 (6·0)
Inclusion criteria			
Fetal abdominal circumference <10th percentile	262 (81·6)	270 (82·1)	354 (78·5)
Estimated fetal weight <10th percentile	296 (92·2)	308 (93·6)	418 (92·5)
Deceleration of Fetal abdominal circumference curve	83 (25·9)	84 (25·5)	95 (21·0)
Fetal abdominal circumference (mm)	287 (278 - 297)	289 (279 - 297)	289 (278 - 299)
Oligohydramnios ╥	87 (31·0)	101 (34·5)	145 (34·4)
Umbilical artery Doppler ‖			
Pulsatility index in the umbilical artery	0·98 (0·85-1·13)	0·93 (0·82-1·10)	0·96 (0·84-1·11)
Absent	7 (2·7)	7 (2·5)	4 (1·0)
Reversed	0	0	1 (0·2)
Cervical length with transvaginal sonography (mm)	30 (22-37)	30 (24-38)	33 (22-41)
Bishop score ≤ 6††	280 (94·0)	293 (97·3)	64 (98·5)

Table shows median (IQR 25th-75th percentile) or number (%).
†: n=275 for induction, n=295 for expectant monitoring, n=364 for non-randomized.
‡ n=304 for induction, n=312 for expectant monitoring, n=413 for non-randomized.
§: n=294 for induction, n=311 for expectant monitoring, n=424 for non-randomized.
╥: n=281 for induction, n=293 for expectant monitoring, n=421 for non-randomized.
‖: n=262 for induction, n=277 for expectant monitoring, n=381 for non-randomized.
: n=299 for induction, n=312 for expectant monitoring, n=31 for non-randomized.
††: n=298 for induction, n=301 for expectant monitoring, n=65 for non-randomized.

Compared with the induction group, women in the expectant monitoring group were more likely to have a Bishop score of less than or equal to 6 and have gestational hypertension, but otherwise the two randomised arms were comparable. Women who declined randomisation were older, had a higher education level, were less likely to smoke, had a lower body mass index (BMI), and were less likely to have a fetal abdominal circumference below the 10th centile. Most women who were randomised met either the fetal abdominal circumference below 10th centile inclusion criterion or the estimated fetal weight below the 10th centile criterion. Only 13 women in the induction group and 10 women in the expectant monitoring group were included because of flattening of the growth curve in isolation.
(Table 1)

Details of the onset of labour are shown in table 2, and pregnancy outcomes are shown in table 3. Trial compliance was good, with induction performed in 306 (95.6%) of the women in the induction group and in only 166 (50.6%) in the expectant monitoring group, resulting in a median time from randomisation to onset of labour of 0.9 days (IQR 0.7 to 1.7) in the induction group and 10.4 days (IQR 5.6

Table 2
Onset of labour

	Induction of labour group (n=321)	**Expectant monitoring group (n=329)**	**Difference in percentage or mean (95% CI)**
Time between randomisation and onset of labour (days)	0•9 (0•7 - 1·7)	10·4 (5·6 - 16·0)	-9·6 (-10·8; -8·5)**
Gestational age at birth (days)	266 (261-271)	277 (269-283)	-9·9 (-11·3; -8·6)**
Onset of labour			
Spontaneous	12 (3·7)	151(46·0)	-42·3 (-48·1;-36·5)**
Planned caesarean section	2 (0·6)	11 (3·3)	-2·7 (-4·9; -0·6)**
Induction	306 (95·6)	166 (50·6)	45·0 (39·2; 50·9)**

Table shows median (IQR 25th-75th percentile) or number (%).** P< 0·001.

Table 3
Pregnancy outcome

	Induction of labour group (n=321)	Expectant Monitoring group (n=329)	Difference in percentage or mean (95% CI)
Mode of Delivery			
Spontaneous	249 (77·6)	257 (78·1)	-0·5 (-6·9; 5·8)
Vaginal instrumental	27 (8·4)	27 (8·2)	0·2 (-4·0; 4·4)
Caesarean section	45 (14·0)	45 (13·7)	0·3 (-5·0; 5·6)
Indications for caesarean section			
Suspected fetal distress (+/- arrest of labour)	37 (82·2)	40 (88·9)	-6·7 (-21·1; 7·8)
Arrest of labour	5 (11·1)	2 (4·4)	6·7 (-4·3; 17·6)
Other	3 (6·7)	3 (6·7)	0·0 (-10·3; 10·3)
Indications for instrumental vaginal delivery			
Suspected fetal distress (+/- arrest of labour)	21 (77·8)	25 (92·6)	-14·8 (-33·3; 3·7)
Arrest of labour	6 (22·2)	2 (7·4)	14·8 (-3·7; 33·3)
Adverse maternal outcome			
Maternal death	1 (0·3)	0	NA
Progression to gestational hypertension	1 (0·3)	6 (1·8)	-1·5 (-3·1; 0·1)
Progression to pre-eclampsia	12 (3·7)	26 (7·9)	-4·2 (-7·7; -0·6) *
Eclampsia, lung-edema, trombo-embolic events	0	0	NA
Abruption placentae (partial)	1 (0·3)	0	NA
Postpartum haemorrhage	10 (3·2)	15 (4·7)	-1·5 (-4·5; 1·5)
Maternal admission‡			
Length of stay in hospital	4·0 (2·0 - 6·0)	4·0 (2·0 - 7·0)	∓

Table shows median (IQR 25th-75th percentile) or number (%).
* P<0·05 ; ∓ P=0·2. (Mann-Whitney test).
‡ n=232 admitted for induction, n=242 admitted for expectant monitoring. NA=not applicable.

to 16.0) in the expectant monitoring group.

Labour was induced in 166 (50.6%) women in the expectant monitoring group: 92 for suspected fetal distress; 21 for hypertensive disorders; 24 on maternal request; nine for prelabour rupture of membranes; five for post-term pregnancy; and 15 for unspecified maternal reasons. Planned caesarean section was performed in

two (0.6%) women in the induction arm: one because of fetal distress, the second because of primary genital herpes infection. A total of 11 (3.3%) women in the expectant monitoring arm had a planned caesarean section: in 10 cases for fetal distress and one for unpredicted breech position. In the expectant monitoring arm, the median time from randomisation to delivery among women who delivered by planned caesarean section was 4.5 days. The numbers of operative and instrumental deliveries were comparable between the groups (27 (8.4%) in the induction group and 27 (8.2%) in the expectant monitoring group).

One (0.3%) woman allocated to induction of labour died at home 10 days after delivery. She had delivered a healthy child vaginally at 38+4 weeks of gestation after spontaneous onset of labour. No cause for her death was found at postmortem and it was classified as a serious unrelated adverse event. No women in the expectant monitoring group died during the study.

Neonatal outcomes are shown in table 4. There were no stillbirths or perinatal deaths. A total of 17 (5.3%) neonates in the induction arm and 20 (6.1%) neonates in the expectant monitoring arm had the primary composite adverse neonatal outcome (difference -0.8%, 95% CI -4.3% to 2.8%). No differences between groups in any of the components of the composite adverse neonatal outcome were found. Median birth weight was lower in the induction group than in the expectant monitoring group (2420 g v 2550 g; difference -130 g, 95% CI -188 g to -71 g; P<0.001). Despite this difference, more fetuses in the expectant monitoring arm had a birth weight below the third percentile (100 (31%) v 40 (13%); difference -18.1%, 95% CI -24.3% to -12.0%; P<0.001).

Table 4
Neonatal outcome

	Induction of labour group (n=321)	**Expectant Monitoring group (n=329)**	**Difference in percentage or mean (95% CI)**
Birth weight (grams)	2420 (2220 – 2660)	2550 (2255 – 2850)	-130 (-188; -71) **
Birth weight percentiles †			
< P 3	40 (12·5)	100 (30·6)	-18·1 (-24·3; -12·0)**
P 3 - P5	82 (25·5)	79 (24·2)	1·3 (-5·3; 8·0)
P5 - P10	88 (27·4)	62 (18·9)	8·5 (-2·0; 14·9)
P10 - P25	88 (27·4)	66 (20·2)	7·2 (0·7; 13·8)
>P25	23 (7·2)	20 (6·1)	-1·1 (-2·8; 4·9)
Composite adverse neonatal outcome	17 (5·3)	20 (6·1)	-0·8 (-4·3; 2·8)
fetal deaths	0	0	
neonatal deaths	0	0	
Apgar score after 5 minutes <7	7 (2·2)	2 (0·6)	1·6 (-0·2; 3·4)
Arterial pH <7·15 ‡	34 (12·2)	38 (13·2)	-1·0 (-6·5; 4·5)
Arterial pH <7·10 ‡	12 (4·3)	19 (6·6)	-2·3 (-6·0; 1·4)
Arterial pH <7·05 ‡	4 (1·4)	10 (3·5)	-2·1 (-4·6; 0·5)
Arterial Base Excess < -10 ‡	16 (5·7)	26 (9·0)	-3·3 (-7·6; 1·0)
Admission to intensive care	9 (2·8)	13 (4·0)	-1·2 (-4·0; 1·6)
Neonatal admission			
Intermediate-care	155 (48·4)	118 (36·3)	12·1 (4·6; 19·7)*
Maternal ward	89 (27·8)	116 (35·7)	-7·9 (-15·0, -0·7) *
No admission	67 (20·9)	78 (24·0)	-3·1 (-9·5; 3·4)
Length of stay			
NICU children	9 (6-14)	13 (6-22)	***
All admissions	4 (2 - 8)	4 (2 - 8)	0·2 (-1·4; 1·8)

Table shows median (IQR 25th-75th percentile) or number (%).
*P<0·05; **P < 0·001; ***P=0.5 (Mann-Whitney test) †: percentiles according to Dutch fetal growth charts (weight related to gestational age).[36]
‡: n=279 for induction, n=288 for expectant monitoring.

The numbers of infants admitted to neonatal intensive care and median duration of stay in unit was comparable between the two groups (9 (2.8%) from the induction group and 13 (4.0%) of the expectant monitoring group; duration 9 days, IQR 6

to 14 and 13 days, IQR 6 to 22, respectively). However, more neonates in the induction group were admitted to a ward providing an intermediate level of neonatal care (155 (48.4%) v 118 (36.3%); difference 12.1%, 95% CI 4.6% to 19.7%; P<0.05). Exclusion of pregnancies complicated by hypertensive disease at randomisation did not alter the results for the composite adverse neonatal outcome or caesarean section (data not shown). Stratified analysis for centre and parity using logistic regression showed no treatment differences among the participating centres (data not shown).

Discussion

This study has shown that among women with a singleton pregnancy complicated by suspected intrauterine growth restriction at a gestational age of between 36+0 and 41+0 weeks, a policy of labour induction neither affects the rate of adverse neonatal outcomes nor the rates of instrumental vaginal delivery or caesarean section.

The present study has only ruled out a difference in adverse neonatal outcomes larger than 4.3%. We have not ruled out an effect on the rarer outcome of perinatal death. One theoretical argument in favour of induction is that it might pre-empt intrauterine fetal death, so clinicians who wish to follow expectant management should monitor the ongoing pregnancy closely.

In our study the number of admissions to neonatal intensive care was comparable in both arms, but more neonates in the induction group were admitted to intermediate levels of care. This finding might be an artefact of the inevitable lower birth weight in this group given that the policy was to admit infants below a certain weight, but complications of late prematurity cannot be ruled out. Limiting induction to infants with a gestational age of greater than 37 weeks would reduce the incidence of this outcome, but we cannot know whether this approach would be associated with better long term outcomes.[27]

The higher median birth weight in the expectant monitoring group indicates that

infants in this group gained on average 130 g during the roughly 10 additional days' gestation they experienced compared with the induction group. Presumably, although most neonates in the present trial were born with a weight below the 10th percentile, a number were not really growth restricted but rather constitutionally small. Constitutionally small infants have the potential to grow at term, whereas growth restricted infants might experience intrauterine undernourishment and decelerated growth. We also observed that the number of children with a birth weight below the third percentile differed significantly between the induction of labour group(12.5%) and the expectant monitoring group (31%).This suggests that a substantial number of children in the expectant monitoring group did not continue to grow along their own expected growth curves. Being born severely growth restricted appears to be associated with worse long term outcomes.[27] Although not defined as a primary outcome in our study, this suggestion could be a compelling reason for induction and certainly merits further investigation.
When women with hypertension or pre-eclampsia at the time of randomisation were excluded, the incidence of the composite adverse neonatal outcome did not differ between the study groups, nor did this result in a lower incidence of caesarean section among women in the expectant monitoring group. Results from the HYPITAT trial support a strategy of inducing women who develop a hypertensive disorder after 37 weeks of pregnancy to prevent possible maternal complications.[22] This probably also applies to women who develop hypertensive disorders in addition to growth restriction, but the number of such women in this trial was too small to investigate this possibility in detail.

Comparison with other studies

Previous observational studies suggest that antenatal detection and induction are associated with an increased incidence of obstetric interventions, without a demonstrable neonatal benefit.[12-14] However, our finding of no effect of induction on adverse neonatal outcomes, which is from a randomised trial, should super-

sede findings from observational studies. The finding that induction did not affect the rate of operative deliveries in our study should also not be surprising because observational studies that suggested an increase in operative intervention with induction have been contradicted by later randomised trials. Observational studies of the effect of induction near term for other fetal indications—such as post-maturity, ruptured membranes, and hypertensive disease—on the rate of operative deliveries have been similarly misleading.[22 28 29]

A similar trial of timed delivery among much more severely compromised pre-term fetuses, the Growth Restriction Intervention Trial (GRIT), was reported in 2004.[30 31] At two year follow-up, the risk of disability was reduced in the delayed delivery group compared with the immediate delivery group among babies younger than 31 weeks of gestation at randomisation. Because growth restriction is associated with a less favourable (neuro)developmental outcome in the term period as well as poor outcomes at delivery,[32] we plan to investigate the wellbeing of the children randomised during DIGITAT at two years follow-up.

Strengths and limitations of study

The main strength of this study is the comparison of randomised groups and the large size of the study population. There have been no other randomised trials in this area.

Identifying fetuses at risk of true intrauterine growth restriction is a diagnostic challenge. Customised growth centile charts[33] are rarely applied in the Netherlands and were not used in the present study, but might identify fetuses at risk. Although we encountered no perinatal deaths among the randomised women, the association between low birth weight and perinatal death is well accepted.[1-4] However, many thousands of participants would be required to power a study on the effects of induction on perinatal death.

The relatively favourable neonatal outcomes in both study groups could reflect the fact that participants and clinicians were more alert to possible complications and

women received cautious attention from their doctors. Monitoring is also intensified in ordinary practice in the Netherlands, but monitoring and therefore neonatal outcomes could have been biased because of the study setting. The study results should be extrapolated with caution to settings where close monitoring cannot be offered.

It was possible to defer delivery in the expectant monitoring group for on average 9.6 days after randomisation, resulting in an average gestational age of 39+3 weeks. Prolongation of gestational age in this group led to more instances of spontaneous vaginal delivery than in the induction group, but did not reduce the number of caesarean sections. Compared with other countries (that is, the United States and the United Kingdom), rates of caesarean section in the Netherlands have always been relatively low,[34] and the rate in this group of high risk pregnancies was even lower than the average rate of 15% in the Netherlands.[25]

The fact that women who declined randomisation were older, more highly educated, and smoked less might suggest that the study recruited a slightly biased group of women. This may have an effect on the generalisability of the results.

Conclusions and policy implications

In conclusion, we found equivalent fetal and maternal outcomes for induction and expectant monitoring in women with suspected intrauterine growth restriction at term, indicating that both approaches are acceptable. In practice, however, obstetricians and patients will let factors other than growth restriction guide decision making at delivery.[35] It is reasonable for patients who are keen on non-intervention to choose expectant management with intensive maternal and fetal monitoring because, as far as we can tell, this approach is safe for the baby. However, it is more rational to choose induction to prevent possible neonatal morbidity and stillbirth on the grounds that we showed no increase in operative and instrumental delivery rates. However, our study was underpowered to show differences in late pregnancy loss.

By inducing labour in cases of intrauterine growth restriction, infants that will not grow any further can be released from their undernourished environment. Future studies should focus on how to distinguish before childbirth fetuses with genuine growth restriction and those that are constitutionally small, and on elucidating which ante partum factors predict adverse outcomes.

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Chapter 5

Neonatal morbidity after induction versus expectant monitoring in intrauterine growth restriction at term – a subanalysis of the DIGITAT RCT.

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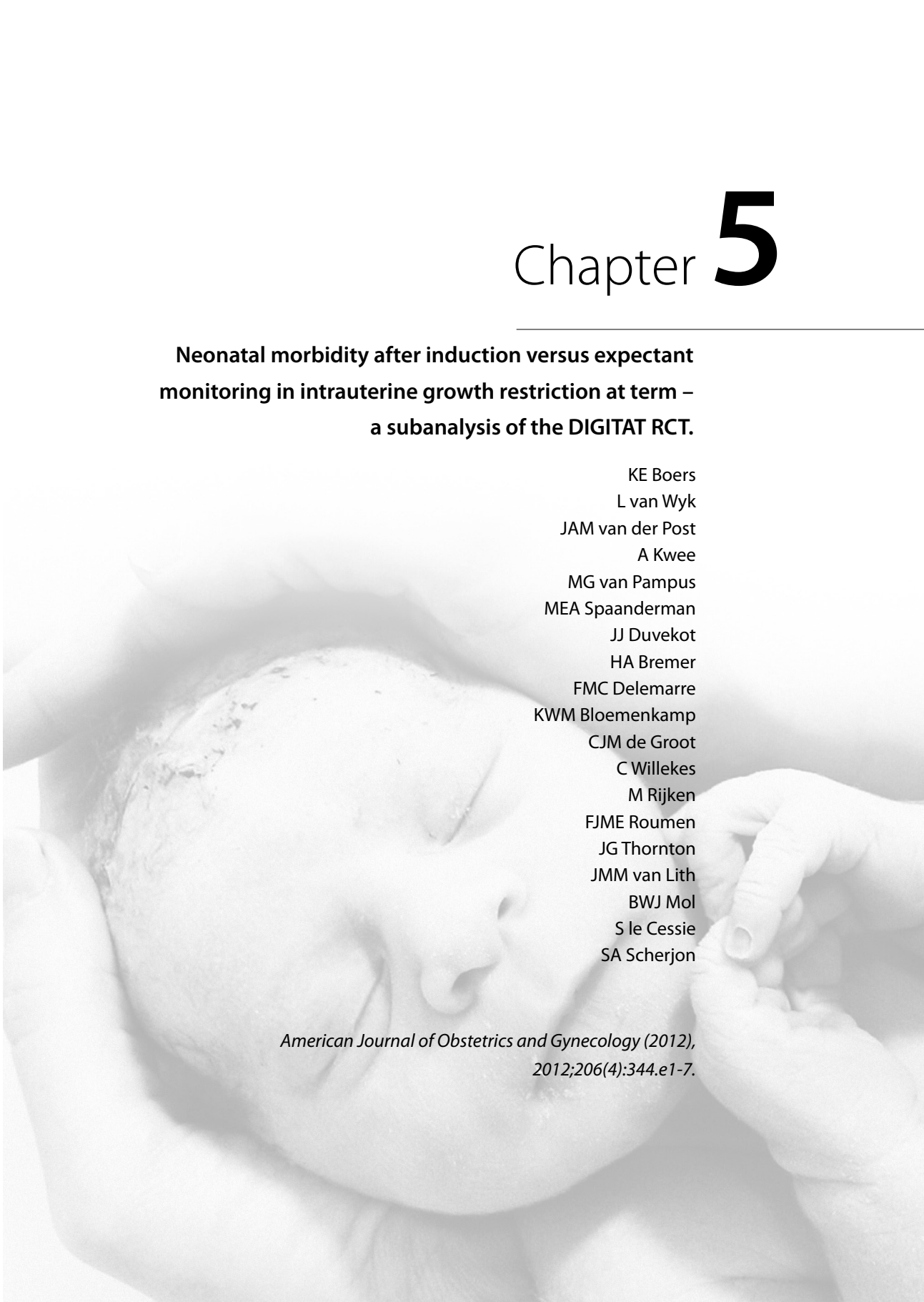
FMC Delemarre
KWM Bloemenkamp
CJM de Groot
C Willekes
M Rijken
FJME Roumen
JG Thornton
JMM van Lith
BWJ Mol
S le Cessie
SA Scherjon



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Abstract

Objective: The DIGITAT-trial compared induction of labor and expectant management in suspected intrauterine growth restriction (IUGR) at term. In this sub-analysis, we report neonatal morbidity between the policies based on the morbidity assessment index for newborns (MAIN).

Study design : We used data from the DIGITAT-trial. For each neonate, we calculated the MAIN score, a validated outcome scale.

Results: There were no differences in mean MAIN scores, nor in MAIN morbidity categories. We found that neonatal admissions are lower after 38 weeks gestational age compared to 36 and 37 weeks in both groups

Conclusions: The incidence of neonatal morbidity in IUGR at term is comparable and relatively mild either after induction or after an expectant policy. However, neonatal admissions are lower after 38 weeks of pregnancy, so if induction to preempt possible stillbirth is considered, it is reasonable to delay until 38 weeks, provided watchful monitoring.

Keywords: Digitat-trial, MAIN score, neonatal morbidity, induction of labor, intrauterine growth restriction at term.

Introduction

AIntrauterine growth restriction is defined as an estimated fetal weight or an abdominal circumference below the 10th centile for gestational age [1]. Postnatally, children with a birth weight below the 10th centile are classified as small for gestational age (SGA). The latter condition is only identified after birth. However, IUGR[2-5] and SGA[6-13] are associated with perinatal morbidity and mortality, even at term. There is no consensus on the management of pregnancies complicated by IUGR.[14-16] We recently performed the Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT)[17] to investigate whether induction of labor for pregnancies with suspected IUGR beyond 36 weeks gestation reduced neonatal morbidity and mortality compared with an expectant approach with fetal and maternal surveillance. Unlike many retrospective studies on growth restriction, our study did not look retrospectively at children being born small for gestational age, but followed children prospectively with suspected IUGR at term.

The study showed comparable primary fetal outcomes (a composite of perinatal death, 5 minute Apgar score below 7, umbilical arterial pH below 7.05 or admission to neonatal intensive care unit (NICU)) as well as comparable rates of operative deliveries. Although the total number of children admitted to intensive care did not differ between the groups, more children in the induction group were admitted to an intermediate level of care than in the expectant group (48% v. 36%, difference 12% [95% CI: 5% to 20%]). Complications of late prematurity[13-18-19] might explain this, since children in the induction group were born on average ten days earlier than in the expectant group, (266 days vs. 277 days, difference -9.9 days, 95% CI: -11 to -9)[17]. However, the difference may simply reflect policies for admission to intermediate levels of care related to prematurity rather than clinically relevant morbidity. It is important to resolve these two competing explanations because, in the expectant group, more children were severely growth restricted, defined as a birth weight below the third percentile (13% v 31%: difference -18% [95% CI -24% to -12%]) and therefore had a possible higher risk of neonatal morbidity.[2-4-6-12] To study the net influence of the two policies on neonatal morbidity in detail, the

MAIN (Morbidity Assessment Index for Newborns) score, a validated outcome measure for neonatal morbidity, was calculated and compared. [20-21]

Subjects and Methods

This is a secondary analysis of the DIGITAT-trial. The original trial was approved by the University of Leiden institutional review board (P04.210). Written informed consent was obtained from all participants before randomization.
The study population consisted of children born to mothers who participated in the DIGITAT-trial. Between November 2004 and November 2008, pregnant women with a singleton fetus in cephalic presentation, and suspected IUGR between 36+0 and 41+0 weeks were recruited. Suspected IUGR was defined as a fetal abdominal circumference (AC) or an estimated fetal weight (EFW) below the 10th percentile, or deceleration of the fetal abdominal circumference in the third trimester.20 Exclusion criteria were previous caesarean section, diabetes mellitus or gestational diabetes requiring insulin therapy, renal failure, HIV seropositivity, prelabor rupture of membranes, severe pre-eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), or a fetus with aneuploidy or congenital abnormalities suspected on ultrasound. Fetuses with decreased or absent movements, and those with abnormal heart rate tracings, were also excluded.
Consenting women were randomly allocated to either induction or expectant monitoring. Participants allocated to the expectant monitoring group were monitored until the onset of spontaneous labor with daily fetal movement counts and twice weekly heart rate tracings, ultrasound examination, maternal blood pressure measurement, assessment of proteinuria, laboratory tests of liver and kidney function, and full blood count. Women were monitored as either an outpatient or an inpatient, according to local protocol. In the expectant monitoring group, induction of labor or planned caesarean section was performed for obstetrical indications—such as suboptimal fetal heart rate tracings, prolonged rupture of membranes, or post maturity between T+7 and T+ 14 days—at the obstetrician's discretion.

Morbidity was calculated using the MAIN score.[20-21] This score was developed

to provide a numeric index of early neonatal outcomes of prenatal care and adverse prenatal exposures in babies delivered beyond 28 weeks of gestation. It is a sensitive and discriminative outcome measure for obstetric clinical trials and is particularly suited for studies with outcomes other than extreme preterm delivery. The data items, such as Apgar scores at 5 and 10 minutes, cord blood pH, hyperbilirubinemia, hypoglycemia, intraventricular hemorrhage and the need for intubation, can all be obtained from the hospital discharge summaries. The final score is divided into four morbidity categories: below 150 (no/minimal morbidity), 151 to 500 (mild morbidity), 501 to 800 (moderate morbidity) and more than 800 (severe morbidity).[21] A MAIN score greater than zero is considered as a positive MAIN score. For children admitted to NICU or intermediate level care, items for the MAIN score were obtained from the discharge summaries. For those discharged home immediately after birth or admitted only to the maternal ward no separate discharge summaries are written, so for them 5 and 10 minute Apgar scores and arterial umbilical artery pH only, were used, assuming that the other items, if not reported were normal.

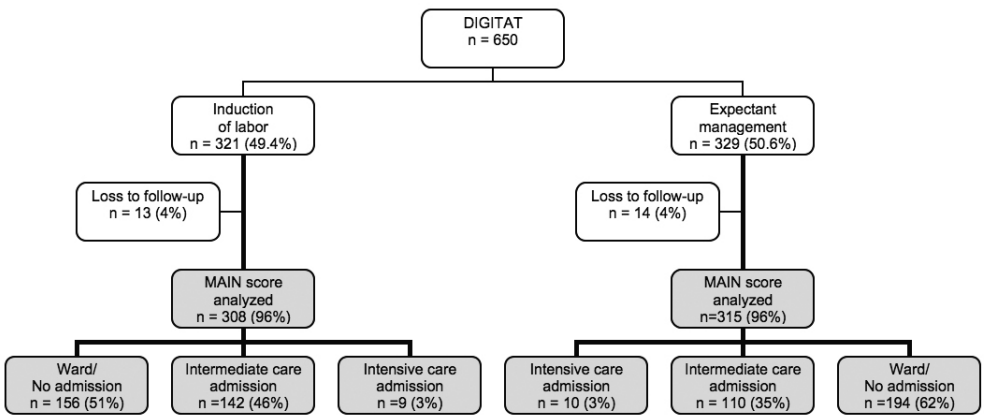
Data were analyzed according to intention-to-treat. Continuous variables were compared using Student's t-test or Fisher exact test when data were normally distributed, or the nonparametric Mann-Whitney U test for skewed data. The chi-square test was used for categorical variables. Treatment effects were presented as difference in percentages with 95% confidence intervals (CI). P-values less than 0.05 were considered to indicate statistical significance. If more than five percent of observations were missing, this was indicated in the footnote of the table. The scores for the induction and expectant groups were compared for all babies and stratified by gestational age at time of randomization and for the different admission types.

We studied the effect of gestational age at randomization on different outcome parameters, such as mean MAIN score, severe MAIN score and composite adverse neonatal outcome. This was done using generalized additive logistic regression models where the effect of gestational age is estimated with a smoothed curve.[22] We tested for differences between the two groups using likelihood ratio tests.

Results

In the DIGITAT-trial, 321 women were randomized for induction and 329 for an expectant management policy (figure 1). The MAIN score was assessed in 308 induction group babies and in 315 expectant management group babies. Baseline characteristics and main trial results are displayed in Table 1.

Figuur 1
Flow diagram of study subjects and their admission categories.



There were no differences between the randomized groups in maternal co-morbidities such as pre-eclampsia or gestational hypertension, heart and vascular disorders or autoimmune disease (data not shown).
As a result of deferring delivery for 10 days with expectant management, gestational age and birth weight differed significantly between the two groups. More babies were admitted to intermediate level of care after induction. No other differences at baseline were found.
Most women who were randomized met either the fetal abdominal circumference below 10th centile or the estimated fetal weight below 10th centile criterion (Table 1.) Only 13 women in the induction group and 10 in the expectant monitoring group were included because of flattening of the fetal abdominal circumference growth curve only.

Table 1
Baseline characteristics of randomized participants as well as main trial results

Characteristic	Induction of labour group (n=321)	Expectant Monitoring group (n=329)	Difference in percentage or mean (95% CI)
Nulliparous	182 (56.7)	201 (61.1)	- 4.4 (-12.0, 3.2)
Maternal age	26.9 (23.3 – 31.2)	27.4 (23.3 – 31.4)	-0.04 (-8.6, 7.8)
BMIa at study entrya	21.9 (19.7 – 25.5)	22.2 (19.7 – 25.6)	-0.1 (-1.0, 0.7)
Maternal smokingb	138 (46.9)	127 (40.8)	-6.1 (-1.8, 14)
Gestational age at randomization (days)	264 (258-269)	264 (258-268)	-0.7, (-2.1, 0.7)
Caucasianc	254 (83.6)	253 (81.1)	- 2.5 (-3.6, 8.5)
Education			
Lower professional school	168 (52.3)	170 (51.7)	0.6, (-7.0, 8.4)
Medium professional school	26 (8.1)	37 (11.2)	-3.1, (-7.7, 1.4)
Unknown	127 (39.6)	122 (37.1)	-2.5 (-5.0, 10.0)
Inclusion criteria			
Fetal abdominal circumference <10th percentile	262 (81.6)	270 (82.1)	-0.5 (-6.4, 5.5)
Estimated fetal weight <10th percentile	296 (92.2)	308 (93.6)	-1.4 (-5.4, 2.5)
Flattening of fetal abdominal circumference curve	83 (25.9)	84 (25.5)	- 0.4 (-6.4, 7.0)
Onset of Labor			
Spontaneous	12 (3.7)	151 (46.0)	- 42.3 (-48.1, -36.5)
Induction	306 (95.6)	166 (50.6)	45.0 (39.2, 50.9)
Elective Caesarean section	2 (0.6)	11 (3.3)	-2.7 – 4.9, -0.6)
Mode of Delivery			
Spontaneous	249 (77.6)	257 (78.1)	0.5 (-6.9, 5.8)
Vaginal instrumental	27 (8.4)	27 (8.2)	0.2 (-4.0, 4.4)
Caesarean section	45 (14.0)	45 (13.7)	0.3 (-5.0, 5.6)
Time between randomization and onset of labor (days)	0.9 (0•7 - 1.7)	10·4 (5·6 - 16·0)	-9.6 (-10.8, -8.5)**
Gestational age at birth (days)	266 (261-271)	277 (269-283)	-9.9 (- 11.3, - 8.6)**
Birth weight (grams)	2420 (2220 – 2660)	2550 (2255 – 2850)	-130 (-188, -71)**
Birth weight by percentile			
< 3rd percentile	40 (12.5)	100 (30.6)	-18.1 (- 24.3, – 12.0)**
3rd – 5th percentile	82 (25.5)	79 (24.2)	1.3 (-5.3, 8.0)
5th to 10th percentile	88 (27.5)	62 (18.9)	8.5 (-2.0, 14.9)
10th to 25th percentile	88 (27.4)	66 (20.2)	7.2 (0.7, 13.8)
>25th percentile	23 (7.2)	20 (6.1)	-1.1 (-2.8, 4.9)
Composite adverse neonatal outcome	17 (5.3)	20 (6.1)	- 0.8 (-4.3, 2.8)
Neonatal admission			
Intensive Care	9 (2.8)	13 (4.0)	-1.2 (-4, 1.6)
Intermediate-care	155 (48.3)	118 (35.9)	12.4 (4.9, 20.0)*
Maternal ward	89 (27.8)	116 (35.7)	-7.9 (-15, -0.7)*
No admission	67 (20.9)	78 (24.0)	-3.1 (9.5, 3.4)

** p < 0·001, * p<0·05
Table shows median (interquartile range 25th to 75th percentile or number (%)).
an=275 for induction, n=295 for expectant monitoring.
bn=294 for induction, n=311 for expectant monitoring.
cn=304 for induction, n=312 for expectant monitoring.
Data were analyzed with the Student t-test or chi-squared test.

The categories of the MAIN scores (no/minimal, mild, moderate and severe morbidity) did not differ between the induction and expectant group. When we looked at components of the MAIN score, more children suffered from hyperbilirubinemia >220 mmol/L or the need for phototherapy after induction of labor (Table 2). In table 2 composite neonatal morbidity (CNM) is shown.

Table 2
Distribution of MAIN score, frequently scored/relevant MAIN items and CNM in the two trial groups110

Morbidity or MAIN score item	**Induction of labour group (n=321)**	**Expectant Monitoring group (n=329)**	**Difference in percentage or mean (95% CI)**
Morbidity according to MAIN score.			
No/minimal (<150)	259 (84.1)	258 (81.9)	-2.2 (-3.7, 8.1)
Mild (151-500)	47 (15.3)	51 (16.2)	-0.9 (-6.7, 4,8)
Moderate (501- 800)	2 (0.7)	5 (1.6)	-0.9 (-2.6, 0.7)
Severe (>800)	0 (0)	1 (0.3)	-0.3 (-0.9, 0.3)
MAIN score item			
Serum bilirubin 251-340 umol/L or phototherapy	32 (10.4)	18 (5.7)	4.7 (0.4, 8.9)*
Apnea and need for oxygena	2 (0.7)	5 (1.6)	-0.9 (-2.6, 0.7)
Assisted ventilation beyond 24ha	0 (0.0)	5 (1.6)	-1.6 (-3.0, -0.2)
Cord blood pH<7.1	11 (3.6)	19 (6.0)	-2.4 (-5.8, 0.9)
Hypoglycemia (glucose concentration < 2.2 mmol/L)	35 (11.4)	34 (10.8)	0.6 (-4.4, 5.5)
Intraventricular hemorrhage grade I or II	0 (0)	1 (0.3)	-0.3 (-0.9, 0.3)
Subdural or intracerebal hematoma	0 (0)	1 (0.3)	-0.3 (-0.9, 0.3)
Composite neonatal morbidity			
Intraventricular hemmorhage	0 (0)	1 (0.3)	-0.3 (-0.9, 0.3)
Periventricular malacia	0 (0)	0 (0)	NA
Proven sepsis	0 (0)	1 (0.3)	-0.3 (-0.9, 0.3)
Nectrotizing enterocolitis	0 (0)	0 (0)	NA
Respiratory distress syndrome	0 (0)	0 (0)	NA
Bronchopulmonary dysplasia	0 (0)	0 (0)	NA

** p < 0·001, * p<0·05, a>2 consecutive readings
Data were analyzed with the Student t-test chi-squared test or Fisher exact test.

When we stratified for different admission types (NICU, Intermediate level care, ward), we also found comparable MAIN scores (Table 3). Stratification for different weight percentiles showed no differences between the MAIN score (Table 3). Five children were admitted to intensive care with a MAIN score of zero.

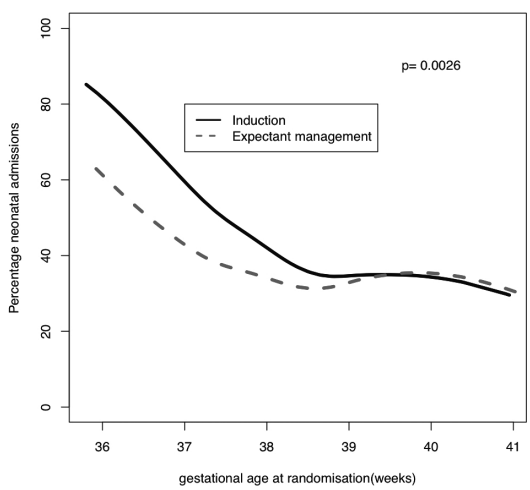
Table 3
Mean MAIN score shown for different admission categories and different growth centiles

	Induction of	**Expectant Monitoring group (n=329)**	**Difference in percentage or mean (95% CI)**
Admission category			
Intensive Care	n=9 118; 136 (0-151)	n=10 363; 203 (101-650)	n=19 - 244 (-520; 31)
Intermediate Care	n=143 88; 0 (0-151)	n=111 104; 98 (0-151)	n=254 -19.26 (-49, 17)
Ward/no admission	n=156 2 ; 0 (0-0)	n=194 6;0 (0-0)	n=350 -4 (8; 1)
Total	n=308 46; 0 (0-0)	n=315 52; 0 (0-0)	n=623 -6 (-24; 12)
Growth centiles			
< p 2.3	n=38 90; 0 (0 – 151)	n=93 85; 0, (0-151)	n=131 5 (-45; 55)
p 2.3 – p 5	n=79 50; 0 (0-103)	n = 74 39; 0 (0-0)	n=153 11 (-18; 40)
p 5 – p 10	n=83 50; 0 (0–0)	n=60 39; 0 (0,0)	n=143 11 (-28; 52)
p 10 – p 75	n=107 23; 0 (0-0)	n=86 34; 0 (0-0)	n=193 -11 (-43;25)
> p 75	n=1 0;0 (0-1)	n=0 NA	NA

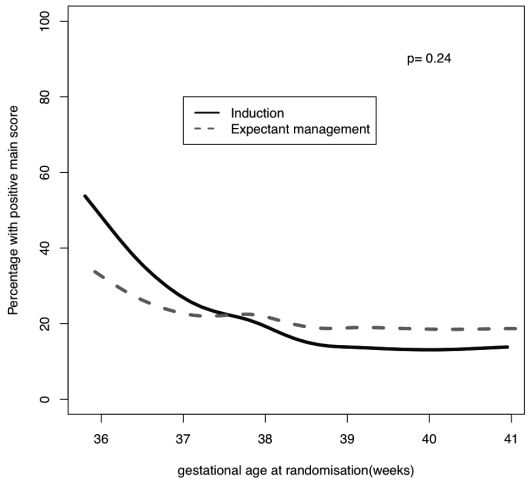
Table shows mean; median (interquartile range 25th to 75th percentile)
Data were analyzed with the Student t-test.

Figure 2 shows the percentage of neonatal admissions related to gestational age at randomization for both groups. Gestational age had a significant effect on the risk of being admitted to neonatal care (NICU and Intermediate level care), with a higher risk at a lower gestational age. The percentage of children admitted to neonatal care was lower after an expectant management. We also compared the percentage of babies born after induction of labor with a positive MAIN score to babies born after an expectant management. Although we found fewer babies with a positive MAIN score beyond 38 weeks randomization as compared to randomization at 36 or 37 weeks, the percentages in the two groups were comparable (Figure 3). In Figure 4 we compared the primary outcome of the trial (composite adverse neonatal outcome; perinatal death, arterial umbilical artery pH below 7.05, 5 minute Apgar below 7 or admission to NICU) in relation to gestational age at randomization. In both the induction group as well as in babies born after expectant management, at the different gestational ages, comparable percentages of composite adverse outcome were found. For all three outcomes (neonatal admissions, positive MAIN score and composite adverse outcome) we compared induction versus expectant management in women randomized before 38 weeks, from 38 till 40 weeks and after 40 weeks. The only difference was a higher percentage of neonatal admissions after induction before 38 weeks gestational age; 125 (61%) admissions vs. 92 (44%) after expectant management, difference 16% ([95% CI: 6.7% to 26%], p=0.001).

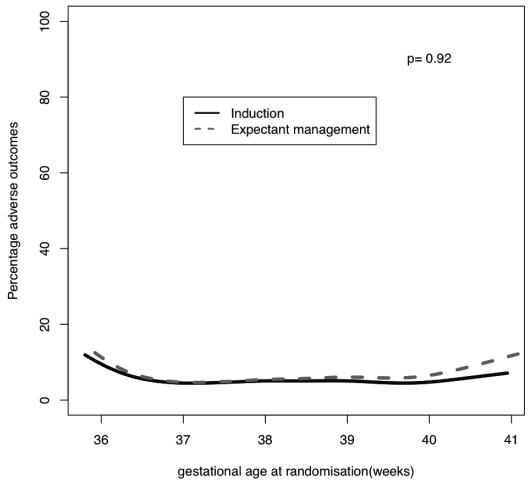
Figuur 2
Gestational age at randomization vs. percentage of neonatal admission.



Figuur 3
Gestational age at randomization vs. percentage of neonates with an adverse composite outcome.



Figuur 4
Gestational age at randomization vs. percentage of neonates with a positive MAIN score.



Discussion

This study confirmed findings of the DIGITAT-trial, where no significant differences in neonatal morbidity between induction and expectant management were found. This supports the hypothesis that the higher rate of admissions after induction of labor was a regular care driven effect of a lower gestational age and lower birth weight, rather than due to defined complications.
Our study was limited to babies suspected of growth restriction at term, which is when most IUGR is detected.[23] In the DIGITAT-trial around 70% of children in fact had a birth weight below the 10th centile, with a higher percentage of very low birth weight (<P2.3) after expectant management. Apparently, the group of patients with suspected growth restriction is mixed, with some babies who are really growth restricted where normal physiological growth is inhibited, and others who are small for gestational age, but grow along their own growth trajectory. Expectant management makes the contribution of those who stopped growing more prominent.
The mean MAIN scores reported in the present study [49] were lower than those published by Verma et al (235).[21] Neonates in our study showed no or minimal morbidity whereas Verma's score indicated mild morbidity for neonates with an IUGR. One explanation is that we limited our study to pregnancies beyond 36 weeks, whereas Verma included neonates from 28 weeks onwards. Another explanation might be that we used discharge summaries, whereas Verma used full hospital records to calculate the MAIN score. Finally, the growth restriction in our population was less severe than the patients included in Verma`s study, that defined IUGR as a birth weight below the 3rd centile.

The fact that five children admitted to the intensive care unit had a MAIN score of zero supports the hypothesis that sometimes admission to intensive care was related to only gestational age or birth weight rather than morbidity. Even though admission to NICU implies serious morbidity, these children were admitted mainly for neonatal observation. For example one child in the expectant management group was admitted to NICU with a birth weight of 1670 grams but no serious morbidity. During the trial, IUGR pregnancies were closely monitored and therefore we can-

not exclude that pregnant women and their babies received more than usual attention because of the setting of the study. The results should not be extrapolated to settings where such monitoring cannot be provided. This monitoring also might explain why our morbidity as defined by MAIN score was relatively mild.
The observation that more babies in the induction group had hyperbilirubinemia is probably explained by being born at an earlier gestational age following an induction policy.[24]
The lack of effect of the induction policy on hypoglycemia, which might have been expected in relatively premature, growth restricted babies might be explained by some neonates born after expectant management getting more severely growth restricted and undernourished, also leading to hypoglycemia. In general, in the expectant management group there was no exclusive neonatal complication that contributed to the MAIN score. However, although not statistically significant, more children were having respiratory problems, which means different and possibly more serious morbidity during expectant monitoring. Two of these children were born with a birth weight above the 10th percentile, which reminds us of the challenges of defining true growth restriction prenatally.
Children born with a low birth weight are prone to develop diseases in later life and associations with metabolic syndrome in adolescence and adult life have been studied extensively.[4] However, the consequences of late prematurity with low birth weight, compared to longer exposure to an undernourished intrauterine environment, on neuro-cognitive and physical development needs to be studied in detail through future follow-up studies.

We found that neonatal admissions were lower after expectant management for those who were randomized before 38 weeks gestational age, while the neonatal admission rates were comparable between both groups after 38 weeks. This suggests that if induction is contemplated the optimal time to do it is around 38 weeks gestational age.

However, in general in pregnancies with IUGR there is an increased risk of stillbirth, with an even higher risk in children with a birth weight below the 3rd percentile [6;17], and we found a higher percentage of these very low birth weights after ex-

pectant monitoring.[18]Therefore in the presence of other pathologic findings, such as abnormal Doppler measurements or abnormalities in fetal surveillance, induction may be implemented at lower gestational ages.

In conclusion, the apparent excess of neonatal care admission in the induction arm of the DIGITAT trial is probably a benign side effect of late prematurity and neonatal admission policies, rather than a marker of serious neonatal morbidity. This means that those who believe for other reasons that induction may pre-empt late stillbirths in this group, can be reassured that such a policy does not appear to increase short-term neonatal morbidity.
If a policy of induction for near term growth restriction is to be followed, deferring induction until 38 weeks, while strictly monitoring mother and child, may prevent complications of late prematurity. Late effects of these policies need further study.

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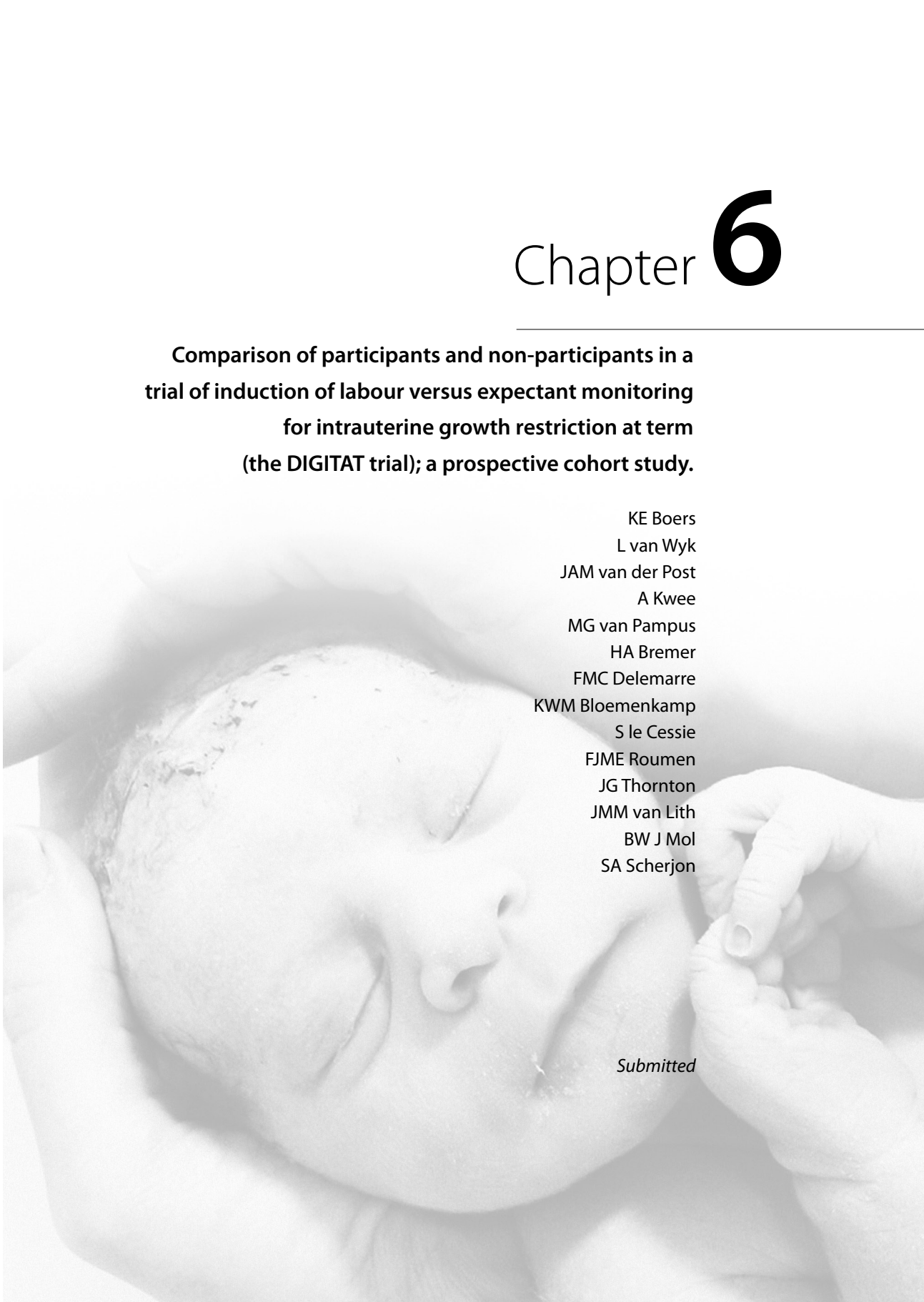
Chapter 6

Comparison of participants and non-participants in a trial of induction of labour versus expectant monitoring for intrauterine growth restriction at term (the DIGITAT trial); a prospective cohort study.

KE Boers
L van Wyk
JAM van der Post
A Kwee
MG van Pampus
HA Bremer
FMC Delemarre
KWM Bloemenkamp
S le Cessie
FJME Roumen
JG Thornton
JMM van Lith
BW J Mol
SA Scherjon



Submitted

Abstract

Objective: The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT) compared induction with expectant management for pregnant women with a suspected growth restricted foetus at term. To measure the external validity of the trial we compared trial participants outcomes with those of non-participants.

Design: Secondary analysis of a randomised equivalence trial (The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT).

Setting: Eight academic and 44 non-academic hospitals in the Netherlands between November 2004 and November 2008.

Participants: Pregnant women who had a singleton pregnancy beyond 36+0 weeks' gestation with suspected intrauterine growth restriction and participated in the DIGITAT trial, and all patients who declined randomisation, but gave authorisation for the use of their medical data. Identical data were collected prospectively.

Main outcome measures: A composite measure of adverse neonatal outcome (neonatal death before hospital discharge, a 5-minute Apgar score < 7, an umbilical artery pH <7·05 or admission to the neonatal intensive care unit), and operative delivery. Comparisons are between participants and non-participants, regardless of the group they are randomised to or treatment received. Propensity scores are used to adjust for baseline differences between the groups.

Results: 650 women were randomised and 452 declined. Non-participants were older, had a lower body mass index (BMI), smoked less frequently and had a higher level of education.
A total of 37 (6%) infants of participants experienced the composite adverse neonatal outcome, compared with 32 (8%) among non-participants (adjusted differ-

ence -2.0% (95% CI -5.2% to 1.1%)). Among non-participants 3 (0.7%) deaths (2 stillbirths, 1 neonatal death) occurred, compared with none in the randomised women (difference -0.7% (95% CI -1.4% to 0.1%), p=0.06). Caesarean sections were performed on 90 (14%) participants and on 71 (16%) non-participants (adjusted difference -2.8% (95% CI -7.5% to 1.8%)). After adjustment for baseline imbalances in maternal age, smoking, BMI, education level and hypertensive disorders the adjusted difference and (95% CI) for perinatal death after participation in the trial was -0.5% ((-1.4% to 0.4%), p=0.27)).

Conclusions: We found a tendency towards better outcomes in participants, even after adjusting for baseline characteristics. Participation in a randomised clinical trial may be good for you.

Introduction

Around 80% of intrauterine growth restricted (IUGR) infants of nulliparae are born at term.[1] Such pregnancies are associated with increased neonatal mortality and short and long term morbidity.[2-8] The DIGITAT trial compared labour induction with expectant monitoring in these pregnancies and showed no important differences in maternal or neonatal outcome.[9-10]

Randomised controlled trials (RCTs) must be internally valid, but to be clinically useful the result must also be relevant to a definable group of patients in a particular clinical setting. Lack of consideration of external validity is the most frequent criticism of RCTs.[11-12] Factors influencing external validity include selection of participating centres and recruitment from primary, secondary or tertiary care. Patient factors affecting external validity include eligibility, exclusion criteria, pre-randomisation diagnosis and the percentage of patients that were non-randomised. Factors related to participation in trials are widely discussed [11-13-15] and women's choice to participate is influenced by preferences and socio-economical background.[13-16-] This inclusion bias might decrease the generalisability of the trial findings.

We used the data of non-participants to assess their characteristics and clinical outcomes and to compare these outcomes to patients who consented to randomisation during the trial. By this means we aimed to determine generalisability of the study outcomes and to detect harmful effects of trial participation.

Methods

Study design and patients

The design of the DIGITAT trial has been described elsewhere.[9] In short pregnant women between 36+0 and 41+0 weeks' gestation who had a singleton fetus in cephalic presentation with suspected intrauterine growth restriction were randomised between induction of labour or expectant monitoring. Suspected intrauterine growth restriction was defined as fetal abdominal circumference below the

10th percentile, estimated fetal weight below the 10th percentile, flattening of the growth curve in the third trimester, or the presence of all three factors.
The trial was run by the Dutch Obstetric Consortium, a collaboration of perinatal centres in the Netherlands, and approved by the University of Leiden institutional review board. Teaching, academic, as well as non-teaching hospitals participated to the trial.
Eligible patients who declined randomisation, but agreed the use of their medical data, were treated according to local protocols at the discretion of the attending obstetrician. Data were collected the same way as for the participants.
Patients who refused randomisation either had induction of labour or an expectant monitoring strategy. The appropriate strategy was in that case elected by the attending obstetrician based on his experience considering the maternal and fetal condition, guided by the preferences of both doctor and patient and local protocols. In the expectant monitoring group of participants labour started either spontaneously, or was initiated by induction for obstetrical indications such as suspected fetal distress, prolonged rupture of membranes, or post maturity between T+7 and T+14 days at the obstetrician's discretion or planned caesarean section.

Statistical analyses

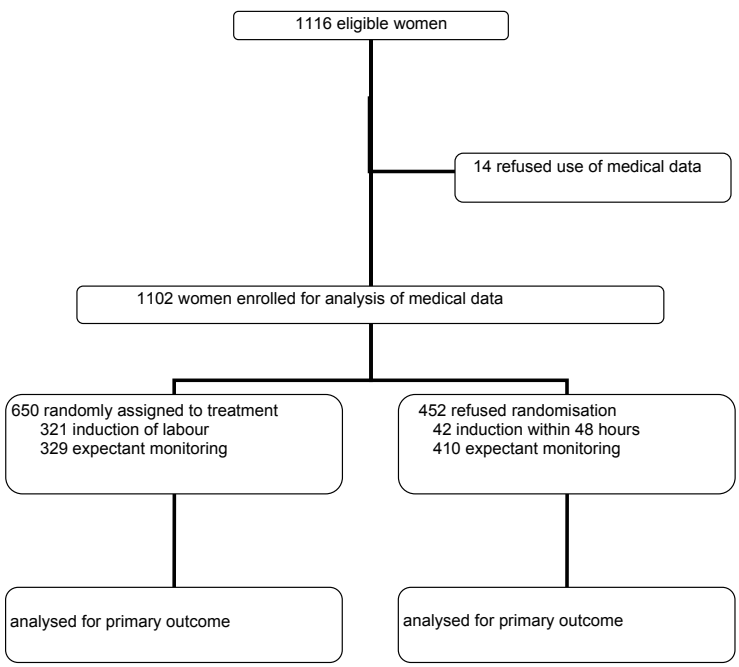
PContinuous variables were summarized as medians with interquartile ranges (IQR). Treatment effects were presented as differences in means or in percentages with 95% confidence intervals (CI). Continuous variables were compared using the Student's t-test or the nonparametric Mann-Whitney U test. The chi-square test and the Fisher exact test were used for categorical variables. If more than 5% of the observations were missing, this is indicated in the footnote of the table. Propensity score methods were used to adjust for group imbalances.[17] The propensity score was calculated for all patients based on the demographic and baseline characteristics using logistic regression. Mean differences and risk differences were adjusted for the propensity score in linear regression models and additive risk models. Multiple imputation was used to handle missing data in the baseline variables. Statistical analysis was performed using SPSS software (version 16•0, Chicago, IL), and R

(version 2.10.0, R Foundation for Statistical Computing, Vienna, Austria.), using the package MICE.[18]

Results

Between 2004 and 2008, 1116 women were eligible, of whom 650 were randomised and 466 declined. Of the 466 women who declined, 452 consented for use of their medical data, of which 410 women were initially monitored expectantly, and 42 had induction of labour within 48 hours (Figure 1).
The baseline characteristics of the participants and the non-participants are listed

Figuur 1
Flow diagram of the process of the study



in Table 1. Participants compared to non-participants were younger (27 years vs. 31 years, mean difference -3.2; 95% CI (-3.9 to -2.6), p<0.001), had a higher BMI (22 vs. 21, mean difference 1.0, 95% CI (0.4 to 1.6), p=0.001), were less educated (84% lower professional education vs. 62% among non-participants, mean difference 23%, 95% CI (16% to 30%), p<0.001) and smoked more (44% vs. 27%, mean difference in percentage 17, 95% CI 11 to 23, (p<0.001).

Pregnancy outcome and mode of delivery are shown in Table 2. Participants were

Table 1
Demographic and baseline characteristics of participants and non-participants patients

Characteristic	IParticipants (n=650)	Non-participants (n=452)	Difference in percentage or mean (95% CI)
Maternal age	27 (23 - 31)	31 (27 - 34)	-3.2 (-3.9 to-2.6) ***
Body mass index at study entry	22 (20-26)	21 (20-24)	1.0 (0.4 to 1.6) **
Gestational age	263 (258 – 269)	262 (258 – 269)	0.9 (-1.0 to 2.7)
Nulliparous	383 (58.9)	275 (60.8)	-1.9 (-7.8 to 3.9)
Caucasian ¥	507 (82.3)	344 (73.3)	-1.0 (-5.7 to 3.7)
Education §			
Lower professional	338 (84.3)	149 (61.6)	22.7 (15.6 to 29.8)***
Higher professional	63 (16)	93 (38)	-22.7 (-29.8 to -15.6)***
Maternal smoking	265 (43.8)	114 (26.9)	16.9 (11.1 to 22.7) ***
Blood pressure at booking (mmHg)			
Systolic	115 (105-120)	115 (110-120)	-0.8 (-2.4 to 0.8)
Diastolic	69 (60-75)	70 (60-75)	-1.2 (-2.4 to -0.1)
Blood pressure at study entry (mmHg)			
Systolic	120 (110-130)	120 (110-130)	-0.8 (-2.6 to 0.9)
Diastolic	72 (65-80)	75 (70-85)	-1.5 (-2.8 to -0.1)*
Women with gestational hypertension	28 (4.3)	25 (5.5)	-1.2 (-3.8 to 1.4)
Women with pre-eclampsia	45 (6.9)	27 (6.0)	0.9 (-2.0 to 3.9)
Foetal abdominal circumference (mm)	288 (278-297)	289 (278-298)	0.9 (-2.1 to 2.3)
Foetal abdominal circumference (mm)	288 (278-297)	289 (278-298)	0.9 (-2.1 to 2.3)

Data are median (IQR 25th-75th percentile) or number (%)
*p<0.05, ** p=0.001, *** p<0.001
¥ (n=616 for participants, n=413 for non-participants)
§ (n=401 for participants, n=242 for non-participants)
(n=605 for participants, n=424 for non-participants)

more often induced, delivered earlier and they tended to deliver spontaneously more often. Significantly more women outside the trial developed gestational hypertension.

Table 3 displays neonatal outcome. More babies of non-participants were severely

Table 2
Pregnancy outcome and onset of labour

	Participants (n=650)	Non-participants (n=452)	Difference in percentage or mean (95% CI)	Adjusted difference in percentage or mean (95% CI)
Time between randomisation and onset of labour (days)	3 (1-11)	8 (3-17)	-3.6 (-4.9 to -2.3)**	-4.3 (-5.4 to -3.2)**
• Induction	1 (1-2)	1 (0-1)		
• Expectant management	10 (5-16)	10 (5-18)		
Gestational age at delivery (days)	271 (263-279)	275 (268-281)	-3.4 (-4.6 to -2.2) **	-3.0 (-4.3 to -1.8)**
• Induction	266 (261-271)	267 (260-273)		
• Expectant management	277 (269-283)	276 (269-282)		
Onset of labour				
Spontaneously	163 (25.2)	197 (43.7)	-18.5 (-24.2 to -12.9)**	-19.4 (-25.5 to -13.3)**
Planned caesarean section	13 (2.0)	13 (2.9)	-0.9 (-2.8 to 1.0)	-1.8 (-3.5 to -0.2)*
Induction	472 (72.8)	241 (53.4)	19.4 (13.7 to 25.1)*	20.9 (14.7 to 27.1)**
Mode of Delivery				
Spontaneously	506 (77.8)	328 (72.7)	5.1 (-0.1 to 11)	4.9 (-0.7 to 10.6)
Vaginal instrumental delivery	54 (8.3)	52 (11.5)	-3.2 (-6.8 to 4.1)	-2.0 (-6.0 to 1.0)
Caesarean section	90 (13.8)	71 (15.7)	-1.9 (-6.2 to 2.4)	-3.2 (-7.8 to 1.5)
Indications for caesarean section				
Suspected fetal distress (+/- arrest of labour)	77 (85.6)	59 (84.3)	2.5 (-8.9 to 13.8)	- 0.2 (-3.5 to 1.9)
Arrest of labour	7 (7.8)	5 (7.1)	0.7 (-7.4 to 8.9)	1.0 (-8.3 to 10.2)
Other	6 (6.7)	6 (8.6)	-1.8 (-10.1 to 6.5)	-2.4 (-12.8 to 7.9)
Adverse maternal outcome				
Maternal death	1	0		
Progression to gestational hypertension	7 (1.1)	13 (2.9)	-1.8 (-3.5 to -0.1)	-2.1 (-3.8 to -0.3)*
Progression to pre-eclampsia	38 (5.8)	38 (8.4)	-2.6 (-5.7 to 0.7)	-1.0 (-4.3 to 2.3)
Postpartum haemorrhage	25 (3.9)	23 (5.1)	-1.2 (-3.7 to 1.3)	- 0.8 (-3.5 to 2.0)
Thrombo embolic events	0	1		
Placental abruption	0	2		

Data are median (IQR 25th-75th percentile) or number (%). CI denotes confidence interval.
* $p < 0.05$; ** $p < 0.001$

growth-restricted (<2.3). There were no significant differences for the other outcomes, but trends were towards more beneficial outcomes for participants. There were no perinatal deaths among participants while there were three deaths among non-participants. Two deaths occurred after expectant policy at 40+1 and at 41+4 weeks pregnancy, with time to delivery of 11 and 24 days respectively. Post-mortem examination showed that these stillbirths were associated with IUGR. The third child died after induction and emergency caesarean section because of placental abruption at 37+2 days gestational age. The suspicion of IUGR had started at 35+6 weeks pregnancy. This child died after a long hospital admission due to serious complications of severe asphyxia. One woman among participants allocated to induction of labour died at home 10 days after delivery. She had delivered a healthy child vaginally at 38+4 weeks of gestation after spontaneous onset of labour. No cause for her death was found at post-mortem and it was classified as a serious unrelated adverse event. No women in the expectant monitoring group of participants or in the non-participants group died during the study.

Table 3
Neonatal outcome

	Participants (n=650)	**Non-participants (n=452)**	**Difference in percentage or mean (95% CI)**	**Adjusted difference in percentage or mean (95% CI)**
Birth weight (grams)	2485 (2235-2750)	2530 (2270-2810)	-28 (-76 to 19)	-19.2 (-70.9 to 32.5)
Percentiles				
< P 2.3a	140 (21.5)	136 (30.1)	-8.6 (-13.8 to -2.3)**	-8.0 (-13.8 to -0.2)*
P 2.3a - P5	161 (24.8)	108 (23.9)	0.9 (-4.3 to 6.0)	- 0.5 (-6.1 to 5.1)
P5 - P10	150 (23.1)	99 (21.9)	1.2 (-3.8 to 6.2)	2.6 (-2.9 to 8.0)
P10 - P25	154 (23.7)	79 (17.5)	6.2 (1.4 to 11.0)*	5.8 (0.6 to 11.1)*
Composite adverse neonatal outcome	37 (5.7)	32 (7.1)	-1.4 (-4.3 to 1.6)	-2.0 (-5.2 to 1.1)
foetal deaths/neonatal deaths	0	3 (0.7)	-0.7 (1.4 to 0.1)	-0.5 (-1.4 to 0.4)
Apgar score after 5 minutes <7	9 (1.4)	10 (2.2)	-0.8 (-2.5 to 0.7)	-1.1 (-2.5 to 0.4)
Arterial pH <7.05 †	14 (2.5)	9 (2.4)	0.1 (-1.9 to 2.1)	0.2 (-2.0 to 2.4)
Admission to intensive care				
Neonatal admission				
High care/Medium care	273 (42.3)	195 (43.2)	-1.1 (-6.9 to 5.0)	-2.7 (-9.3 to 3.8)
Maternal ward	205 (31.8)	130 (28.8)	3.0 (- 2.6 to 8.5)	2.1 (-3.9 to 8.2)
No admission	145 (22.5)	110 (24.4)	-1.9 (-7.0 to 3.2)	1.6 (-3.9 to 7.1)
Length of stay (days)	4 (2-8)	4 (2-7)	∓	0.3 (-1.0 to 1.6)

Data are median (IQR 25th-75th percentile) or number (%).
CI denotes confidence interval.
a= severe growth restriction according to Dutch percentiles

* p <0.05, **p <0.001 ∓ p=0.5 (Mann-Whitney test)
† n= 567 for participants, n=377 for non-participants
percentiles according to Dutch fetal growth charts

Discussion

In this study comparing the clinical course of women diagnosed with suspected growth restriction at term, we could not identify harmful effects from participation in a randomised trial comparing induction and expectant management.

The strength of this study is that data were collected prospectively in an identical way, both from participants and non participants.

Though the median fetal abdominal circumference at baseline was comparable for participants and non-participants we found a higher rate of severely growth restricted children at birth in non-participants. Besides, we found a trend towards less spontaneous deliveries and worse neonatal outcomes (more perinatal mortality and lower Apgar scores).

Non-participants were healthier at baseline on important clinical characteristics (i.e. BMI, educational level and smoking). Although these characteristics are in general associated with better neonatal outcomes,[19] opposite associations have been observed in low birth weight infants, like lower mortality rates in low birth weight infants with smoking mothers.[20] This so-called birth weight paradox can be explained by the fact that smoking causes IUGR in otherwise healthy infants, while IUGR in non-smoking women is caused by other medical reasons. Adjusting for the baseline differences between participants and non-participants did not change the results.

Most non-participants were managed initially with an expectant policy, suggesting that this was the preferred management policy of most obstetricians and women during the trial period.

An important difference between the participants and non-participants is that non-participants probably had a strong preference for one of the two management strategies, while the participants were willing to undergo both strategies.

A possible explanation for declining randomisation could be the fact that women did not want to be induced out of fear for medical interventions. Although fewer women that declined participation were induced, this did not lead to a lower rate of operative deliveries.[21]

Our data are in accord with many other studies which suggest that participation in a randomised trial[22] or protocol driven management[23] improves outcomes regardless of the actual treatment given.[14-16-24] It seems that the DIGITAT women benefited from the protocol-driven attention of their doctors. Moreover women participating in a study are probably also more attentive to their medical status.

Recruitment to clinical trials is influenced by social economic status (SES), and women who are less educated are often less willingly to participate.[25-30] Conversely, in the DIGITAT trial a lower SES led to more participation.

Overall neonatal admission rates were comparable in the two groups, but more children of non-participants were severely growth restricted at birth, probably as a result of a longer expectant time to delivery. This is in accord with results of the DIGITAT trial. The higher rate of severe growth restricted children might explain the tendency towards less favourable outcomes. However, we did not find this association between severely growth restricted children and worse outcomes among children of participants who were managed expectantly.[31]

While none of the children of participating women died, perinatal deaths did occur among non-participants. The mutual factor of these 3 children was a relative long time of expectant management, and 2 of the 3 were delivered only after 40 weeks. These findings might imply that over long prolongation of pregnancy in IUGR imposes perinatal morbidity and mortality, perhaps also due to the lack of protocol driven management.

In conclusion we found a tendency towards more favourable outcomes in women randomised to the DIGITAT trial than in women who refused to participate, even after adjusting for baseline characteristics. Participation in a randomised clinical trial on growth restriction did not increase the risk of bad outcome.

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Chapter 7

Maternal health-related quality of life after induction of labor or expectant monitoring in pregnancy complicated by intrauterine growth retardation beyond 36 weeks

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Qual Life Res. 2011; 20(9): 1427- 36

Abstract

Objective: Pregnancies complicated by intrauterine growth retardation (IUGR) beyond 36 weeks of gestation are at increased risk of neonatal morbidity and mortality. Optimal treatment in IUGR at term is highly debated. Results from the multicenter DIGITAT (Disproportionate Intrauterine Growth Intervention Trial At Term) trial show that induction of labor and expectant monitoring result in equal neonatal and maternal outcomes for comparable cesarean section rates. We report the maternal health-related quality of life (HR-QoL) that was measured alongside the trial at several points in time.

Methods: Both randomized and non-randomized women were asked to participate in the HR-QoL study. Women were asked to fill out written validated questionnaires, covering background characteristics, condition-specific issues and the Short Form (SF-36), European Quality of Life (EuroQoL 6D3L), Hospital Anxiety and Depression scale (HADS), and Symptom Check List (SCL-90) at baseline, 6 weeks postpartum and 6 months postpartum. We compared the difference scores of all summary measures between the two management strategies by ANOVA. A repeated measures multivariate mixed model was defined to assess the effect of the management strategies on the physical (PCS) and mental (MCS) components of the SF-36. Analysis was by intention to treat.

Results: We analyzed data of 361 randomized and 198 non-randomized patients. There were no clinically relevant differences between the treatments at 6 weeks or 6 months postpartum on any summary measures; e.g., on the SF-36 (PCS: P =0.09; MCS: P =0.48). The PCS and the MCS were below norm values at inclusion. The PCS improved over time but stayed below norm values at 6 months, while the MCS did not improve.

Conclusions: In pregnancies complicated by IUGR beyond 36 weeks, induction of labor does not affect the long-term maternal quality of life.

Introduction

Pregnancies complicated by intra-uterine growth retardation (IUGR) are at increased risk for adverse neonatal outcome. Suspected IUGR often results in small-for gestational age (SGA) neonates, perinatal mortality and morbidity, and adverse long-term health of the child [1-5]. IUGR is associated with hypertensive complications in pregnancy. Delivery to release the fetus from its nutritionally inadequate environment is thought to be the only feasible treatment [6-7]. However, there is no consensus regarding the optimal management strategy in IUGR at term. Induction of labor is believed to result in a higher chance of complications during delivery, while expectant monitoring provides a maximal chance of spontaneous labor at the expense of possible complications for the child.

We recently compared induction of labor and expectant monitoring in women with an IUGR-fetus beyond 36 weeks of gestation in a nationwide randomized clinical equivalence trial called DIGITAT (Disproportionate Intrauterine Growth Intervention Trial At Term; ISRCTN10363217). Results indicated that both treatments result in equal neonatal and maternal outcomes [8-9]. Alongside the DIGITAT trial, we conducted a health-related quality of life (HR-QoL) study to examine the impact of the non-invasive (expectant monitoring) and the assumed invasive (induction of labor) strategy on the mother's self-reported health as a secondary outcome. Given the observed clinical equivalence, maternal outcomes gain importance to support clinical decision-making. HR-QoL can be an important factor for women to choose one treatment over the other and may lead to better treatment satisfaction.

We compared the impact of the two strategies at six weeks and at six moths postpartum in terms of self-reported health, anxiety, depression, and physical and mental symptoms, using validated questionnaires. The DIGITAT HR-QoL study includes observational data on patient outcome from patients refusing to participate in the trial to address potential bias from trial participation. We hypothesized that the invasive strategy would be more burdensome, as it was expected to be associ-

ated with a higher intervention rate such as instrumental delivery and caesarean sections.

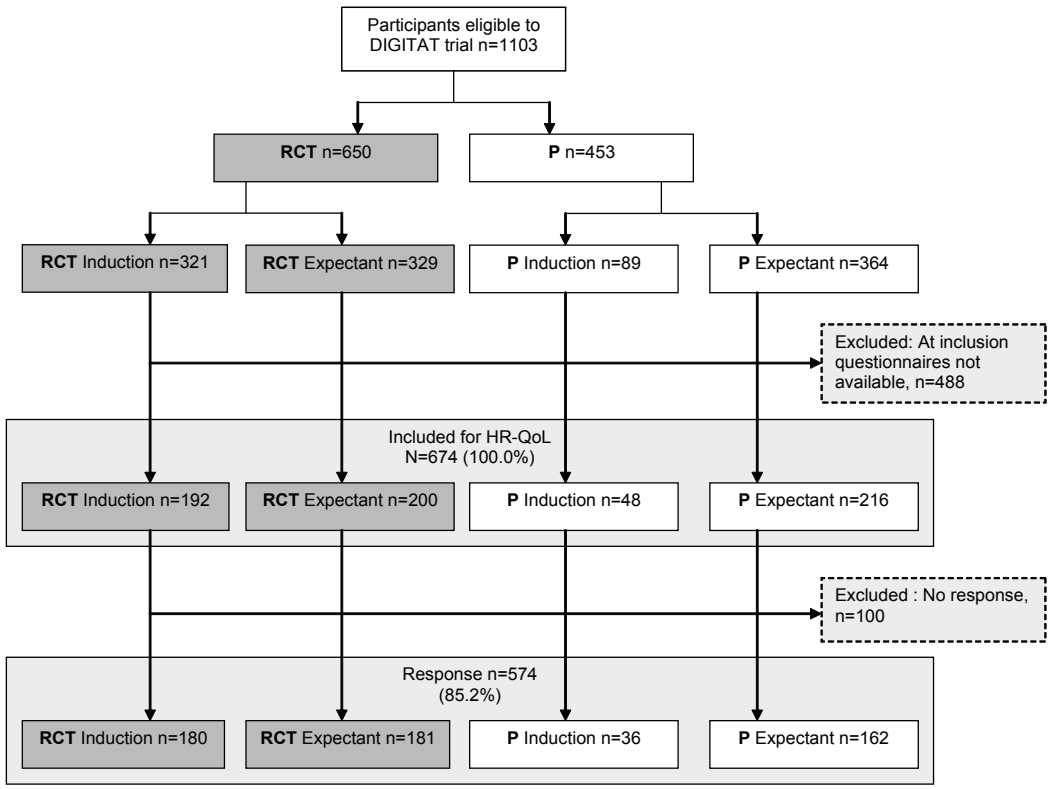
Methods

Patients and clinical study

In the equivalence DIGITAT trial, primary outcome was defined as a composite neonatal adverse outcome, defined as death before hospital discharge, 5-minute Apgar score < 7, umbilical artery pH < 7·05, or admission to the neonatal intensive care. Eligible patients were women with a singleton pregnancy and a fetus in cephalic presentation between 36+0 to 41+0 weeks gestational age, with suspected IUGR. IUGR was defined as fetal abdominal circumference below the 10th percentile, estimated fetal weight below the 10th percentile and/or a decreased relative growth. Exclusion criteria were maternal age below 18 years, previous caesarean section, ruptured membranes, diabetes mellitus, renal disease, seropositivity for HIV, and HELLP syndrome (Hemolysis Elevated Liver enzymes, Low Platelet count) upon presentation. Women who refused randomization were included in the study as non-randomized patients. Details of the study design have been described elsewhere [8;9]

All eight academic and 44 non-academic Dutch hospitals participated in the DIGITAT trial. The trial was approved by the Institutional Review Board of the University of Leiden (P170-99) and had local approval from the boards of the other participating hospitals. Women who were eligible for inclusion in the DIGITAT study received study information from a research nurse, midwife, resident, or gynecological staff member. Written informed consent was obtained from all patients prior to participation. Patients were randomly assigned to either induction of labor or expectant management. For logistic reasons the inclusion for the HR-QoL study started July 2005, 8 months after the start of the clinical trial; the last HR-QoL patient was included October 2008. Individual and aggregate HR-QoL results were not made available at any stage during the study. Figure 1 shows a flowchart of the study.

Figure 1
Flowchart. HR-QoL = Health-related Quality of Life; RTC = randomized controlled trial; P = treatment following protocol.



Clinical interventions and procedure

In women allocated to induction, labor was initiated within 48 hours after randomization. Patients with a Bishop score >6 were induced for labor by amniotomy and, if needed, augmented with oxytocin. Patients with a lower Bishop score were primed with prostaglandins. In women allocated to the expectant group fetal condition was monitored frequently during hospital or home-care admittance or in an outpatient setting, i.e. fetal movements as reported by the mother, electronic fetal

heart rate monitoring, and biophysical profile by ultrasound if indicated. Induction of labor was recommended in case of fetal distress; i.e. non-reassuring fetal heart rate, or decreased or absent fetal movements. Amongst others, reasons for induction were prolonged rupture of membranes, pre-eclampsia, and post-term pregnancy. The study protocol has been described in more detail elsewhere [8-9].

Background characteristics and clinical data (obstetric history, medical treatment, maternal and neonatal outcome, and interventions during hospital stay) were collected by local research midwives or nurses using a web-based case record form. Data on maternal and neonatal mortality and morbidity as well as diagnoses at discharge were collected until six weeks postpartum. Outcomes of the DIGITAT trial indicated that the medical outcomes were equivalent between induction of labor and expectant management for composite adverse neonatal outcomes (resp. 6.1% versus 6.9%; 95% CI -4·9%; 3·2%), caesarean section rate (resp. 14.0% versus 13·7%; 95% CI -5·0%; 5·6%) (9).

HR-QoL measures

The participating women received a folder containing instructions, four HR-QoL questionnaires to be completed at baseline before inclusion/randomization (B1), at baseline after inclusion/randomization (B2), 6 weeks postpartum (6W), and 6 months postpartum (6M). Each questionnaire took between 10 and 30 minutes to complete. Four pre-stamped return envelopes, and reminder stickers –the women could stick these stickers in their agenda or on their calendar as a self-reminder for filling out a questionnaire on the appropriate date. The folders, including the questionnaires, were available in the Dutch and English languages. Patients who did not return questionnaire 6W within 7 weeks after delivery or questionnaire 6M within 7 months after delivery received a written reminder and a new copy of the questionnaire with a pre-stamped return envelope.

Questionnaire B1 contained questions on background characteristics, e.g. date of birth, educational level, employment characteristics, household composition, ob-

stetric history, ethnicity, length, and weight before pregnancy. Questionnaire 6W contained the retrospectively report of pain after delivery at day 1, 4, and 7 after delivery, using a 4-point pain intensity scale and an 'I don't know' option. All questionnaires involved validated measures which will be elucidated below. We have used the Medical Outcome Study 36-Item Short Form Health Survey (SF-36; applied to questionnaires B1, 6W, 6M), the European Quality of Life 6 dimensions 3 levels (EuroQoL 6D3L) with subsequent general health Visual Analogue Scale (VAS; questionnaires B2, 6W, 6M), the Hospital Anxiety and Depression Scale (HADS; questionnaires B2, 6W, 6M), and the Symptom Check List (SCL-90; questionnaire 6M); all measures have been validated in Dutch and English [10-16].

The SF-36 is a generic questionnaire with eight health-status subscales: physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health, and general mental health. The scores on the subscales are aggregated into the standardized summary scores Physical (PCS) and Mental Component Score (MCS). A standardized score of mean=50 and SD=10 represents the Dutch population average [10;11]. The EuroQoL 6D3L is an instrument to describe general health status with six dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and cognitive functioning). An individual's (or population's) health description can be expressed in a value between 0 (death) and 1 (perfect health) [12;17]. The subsequent VAS in our study is a vertical scale ('thermometer') with values 0 'worst possible health state' (lower anchor) to 100 'best possible health state' (upper anchor). Patients indicated their health state by marking the VAS, while considering the anchors [18]. The HADS is a self-report instrument that exists of two 7-item scales: one for anxiety and one for depression each with a score range of 0 to 21; a lower score indicating less anxiety or depression [14-19]. Finally, the SCL-90 is a 90-item inventory that is used to measure the psychological symptom status. The SCL-90 exists of one overall score and eight symptom subscales: anxiety, agoraphobia, depression, somatic complaints, insufficiency of acting and thinking, interpersonal sensitivity, hostility, and sleeping problems. Higher scores indicate

worse health [16-20]. Because the SCL-90 is a long and demanding measure, we decided to apply the SCL-90 only in the 6M questionnaire.

Analysis

If induction of labor would be more burdensome, we would expect a differential impact of intervention strategy on the HR-QoL measures, where induction of labor results in a lower HR-QoL. Prior to analysis we checked for the presence of selective response regarding neonatal outcome, maternal outcome, and mode of delivery; i.e. overrepresentation of either very healthy or very unhealthy patients in our sample. We defined 'adverse neonatal outcome' as the presence of any of the following: fetal death, 5-minute Apgar score <7, umbilical artery pH <7.05, admission to neonatal intensive care unit, and/or neonatal death (8-9). We defined 'adverse maternal outcome' as admission to the medium care or intensive care unit [8-9].

Regarding short-term differences between the randomized induction of labor and expectant management groups, we analyzed the retrospectively self-reported 4-point scale pain intensity after delivery using Mann-Whitney's U.

Then, we compared the impact of treatment strategy (following intention to treat) on HR-QoL for the randomized and non-randomized groups separately on the summary measures of the SF-36 (separate report on subscales PCS and MCS), EuroQoL (Mobility, Self-care, Activity, Pain/Discomfort, Anxiety/Depression), VAS General Health, and the HADS (Anxiety, Depression). HR-QoL improvement was defined as the difference score between the baseline and a postpartum measurement. The difference scores were statistically compared between treatment strategies using Student's t-test for each measurement separately.

The HR-QoL impact on the SCL-90 summary scores (anxiety, agoraphobia, depression, somatic complaints, insufficiency of acting and thinking, interpersonal sensitivity, hostility, and sleeping problems) at 6 moths post partum was addressed with Student's unadjusted t-test between the randomized intervention strategies.

To explain the changes over time on the 'physical' SF-36 PCS and the 'mental' SF-36 MCS scales, we applied a repeated measures linear mixed model with the following explanatory components: time of assessment (baseline; 6 weeks postpartum; 6 months postpartum), intervention strategy following intention to treat (expectant; induction), randomization (no; yes), age (≤27; 28-33; ≥34), ethnicity (indigenous/non-indigenous), pre-pregnancy BMI (underweight; normal weight; overweight), parity (nulliparous, multiparous), educational level (lower; higher), and the interaction terms time of assessment*randomization, and time of assessment*intervention strategy.

Analyses were conducted using SPSS 15.0 for Windows (SPSS Inc, Chicago, IL). A p-value of <0.05 (two sided) was considered to indicate statistical significance. We used post hoc Bonferroni adjustment to adjust for multiple testing.

Results

Baseline characteristics

Of the 1102 participants to the DIGITAT study, 650 (56%) were randomized whereas 453 (44%) women participated in the non-randomized part of the study. Not all patients were asked for participation because of logistic reasons because study material was not in stock in every hospital; however, this did not lead to systematical exclusion of any patient group to the HR-QoL study. Of the randomized patients, 392 (60%) were asked to participate in the HR-QoL study, versus 264 (58%) of the non-randomized patients. Overall, 574 (85%) of the patients that were included in the HR-QoL study responded to at least one questionnaire (Figure 1). Response rates were 95%, 83%, 72% and 59% for questionnaires B1, B2, 6W, and 6M, respectively.

Baseline characteristics of the randomized and non-randomized HR-QoL participants, and of the responding and non-responding patients (i.e. patients who did

not respond to any questionnaire) are shown in Table 1.

Table 1
Baseline characteristics of the randomized (Rand) and non-randomized (NRand) participants who followed induction of labor or expectant monitoring, and the patients who did not return the HQRL questionnaires (Non-response); analyses of the randomized vs. non-randomized and responses vs. non-responses.

	Response, N=574							
	Induction Rand n=180	Expectant Rand n=181	Induction NRand n=36	Expectant NRand n=162	Total Response N=574	Non-response n=100	Randomized vs Non-Rand p	Response vs Non-response p
Age: mean (SD)	28.0 (5.2)	28.0 (5.2)	31.2 (4.4)	31.8 (4.9)	29.3 (5.4)	29.5 (5.9)	<.001	.680
Months to conceive: mean (SD)	9.0 (16.7)	9.9 (18.0)	9.9 (19.1)	7.5 (10.0)	8.8 (15.3)	n/a a	.355	n/a
BMI pre-pregnancy: mean (SD)	23.3 (5.3)	23.4 (5.2)	22.3 (4.9)	22.3 (4.0)	23.0 (3.9)	22.8 (4.6)	.003	.511
Dutch origin: %	89.0	86.4	90.6	84.5	87.2	59.0	.071	<.001
Has a job: %	74.9	75.0	80.6	87.8	79.2	n/a	.001	n/a
Lives with partner: %	88.6	88.8	90.6	93.4	90.4	n/a	.071	n/a
Nulliparious: %	58.6	58.5	51.6	61.4	59.3	57.0	.417	.369
High educational level b: %	15.6	18.6	25.8	43.5	25.9	18.0	<.001	.230
Smoking c: %	45.4	38.0	24.4	25.1	32.0	37.1	<.001	.205

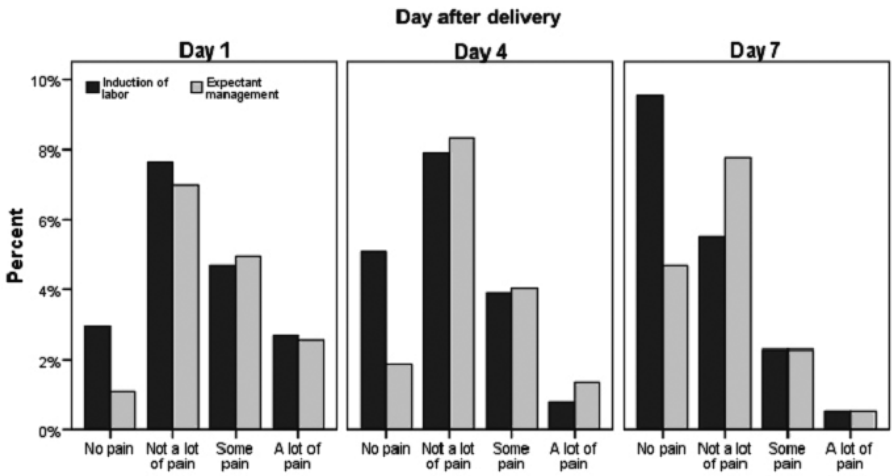
a These values are not available because they were asked by HR-QoL questionnaire
b Higher vocational training or university
c Did not quit smoking before the second trimester

We tested for selective response regarding maternal outcome, neonatal outcome, and mode of delivery. At 6 weeks postpartum there were no significant differences between responding and non-responding patients in the proportion of composite bad neonatal outcome (14.9% vs. 10.2%; p=.052), the proportion of composite bad maternal outcome (3.7% vs. 1.7%; p=.156), caesarean section rates (13.1% vs.15.1%; p=.280), and the proportion of assisted vaginal delivery (11.4% vs. 8.1%; p=.109). At 6 months postpartum there were also no differences between responding and non-responding patients in the proportion of bad composite neonatal outcome (14.4% vs. 10.4%; p=.083), the proportion of bad composite maternal outcome (3.9% vs. 1.4%; p=.090), caesarean section rates (13.1% vs. 15.3%; p=.251), and the proportion of assisted delivery (10.8% vs. 8.4%; p=.192). These results are not tabulated.

Self-reported pain after delivery

There were differences on the retrospectively self-reported pain at day 4 (p=.006) and 7 (p=.003) after delivery between the randomized groups in favor of induction of labor. Figure 2 shows the pain distributions at day 1, 4, and 7 after delivery per randomized group.

Figure 2
In retrospect self-reported pain at day 1, 4, and 7 after delivery between the randomized induction of labor and expectant management group.



Summary measures

One-way ANOVA analyses between the average difference scores of the two randomized groups at 6 weeks and 6 months postpartum are shown in Table 2.

At 6 weeks postpartum, only the average difference scores of the SF-36 PCS between the randomized groups were statistically, but not clinically, different (8.99 vs. 6.49; p=.049). At 6 months postpartum, only the average differences on the EuroQoL Pain and Discomfort domain was statistically, but also not clinically, different between the randomized groups (0.007 vs. 0.031; p=.021).

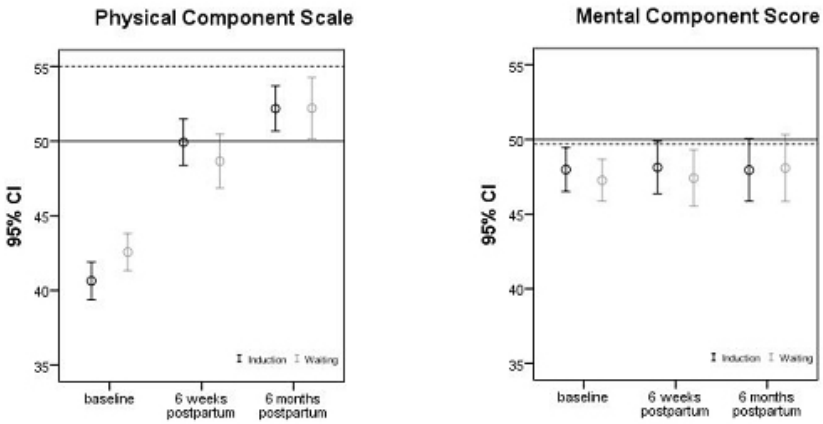
Mean difference scores between the non-randomized groups did not differ significantly either at 6 weeks and at 6 months postpartum. After Bonferroni adjustment none of the outcomes were significant.

Table 2
Average HR-QoL difference scores (Δ) per summary measure: comparisons between randomized groups (Rand) and between non-randomized (Nonrand) groups (Ind=induction of labor; Exp=expectant monitoring) at 6 weeks and 6 months postpartum.

	Δ inclusion, 6 weeks postpartum (Rand), n=241			Δ inclusion, 6 months postpartum (Rand), n=198			Δ inclusion, 6 weeks postpartum (NonRand), n=139			Δ inclusion, 6 months postpartum (NonRand), n=118		
Summary measure	**Ind**	**Exp**	**p**	**Ind**	**Exp**	**P**	**Ind**	**Exp**	**P**	**Ind**	**Exp**	**p**
SF-36 PCS	8.99	6.49	.049	11.80	9.72	.121	4.73	6.74	.295	12.06	11.62	.832
SF-36 MCS	-1.32	-1.14	.894	-0.67	-0.21	.784	-4.11	-1.22	.185	-3.10	0.76	.086
EuroQoL Mobility	0.017	0.023	.367	0.017	0.033	.102	0.036	0.017	.191	0.044	0.022	.196
EuroQoL Self-care	0.014	0.010	.336	0.015	0.013	.536	0.007	0.009	.772	0.007	0.010	.751
EuroQoL Activity	0.048	0.047	.988	0.049	0.053	.727	0.031	0.044	.373	0.048	0.060	.492
EuroQoL Pain/Discomfort	0.018	0.027	.356	0.007	0.031	.021	0.015	0.10	.660	0.009	0.009	.969
EuroQoL Anxiety/Depression	0.008	0.004	.527	0.006	0.005	.898	0.016	0.011	.558	0.020	0.007	.336
VAS general health	1.02	2.09	.649	0.64	4.17	.149	4.75	2.98	.497	8.67	4.15	.143
HADS Anxiety	-1.58	-1.74	.761	-1.12	-1.28	.786	-0.50	-0.51	.989	-0.61	-0.33	.740
HADS Depression	-1.13	-1.90	.105	-0.87	-1.74	.131	-0.32	-0.88	.368	-0.88	-0.84	.962

Figure 3 shows the mean scores of the SF36 PCS and MCS for the randomized groups at baseline, 6 weeks postpartum, and 6 months postpartum. The PCS increased substantially over time between baseline and 6 weeks (PCS scores 41.6 vs. 49.3; p=.038) and between 6 weeks and 6 months postpartum (49.3 vs. 52.2; p=.045); the PCS was higher than the Dutch population average at 6 months postpartum. The MCS did not vary significantly over time between baseline and 6 weeks (MCS scores 47.6 vs. 47.8; p=.559) and between 6 weeks and 6 months postpartum (47.8 vs. 48.0; p=.615). The average MCS score remained below the Dutch population norms (solid line) [11] and both the PCS and MCS remained below the U.S. norms for females between 25 and 35 years old (dotted line) [21].

Figure 3
Error bars with 95% confidence interval (CI) of the randomized groups for induction of labor or expectant monitoring on the PCS and MCS at inclusion, at 6 weeks postpartum, and at 6 months postpartum. The horizontal lines indicate mean Dutch population norm scores (solid line) and U.S. population norm scores for females aged 25 to 34.



At 6 months postpartum there were no HR-QoL differences between the induction of labor and the expectant management (randomized) groups on the SCL-90 summary score (p=.711), or on its sub-scores Anxiety (p=.756), Agoraphobia (p=.884), Depression (p=.909), Somatic complaints (p=.483), Insufficiency of acting and thinking (p=.608), Interpersonal sensitivity (p=.888), Hostility (p=.792), and Sleeping problems (p=.914). These results are not tabulated.

Multivariate mixed model

Table 3 shows the results of the multivariate mixed model explaining the change of PCS and MCS over time, taking some background characteristics and intervention features into account. The β-coefficients represent the change in the dependent variable when the covariate changes with one unit of measurement. PCS improved substantially after childbirth (6 weeks postpartum: β=5.84, p<.001; 6 months postpartum: β=10.65, p<.001). The MCS did not vary over time (6 weeks postpartum: β=-0.77, p=.557; 6 months postpartum: β=1.73, p=.241). There was no effect of

randomization (i.e. participating to the trial as a randomized patient or a non-randomized patient) on PCS (β=-0.62, p=.493), or MCS (β=1.09, p=.376). Intervention according intention to treat was not significant on either PCS (Induction of labor: β=-1.47, p=.090) or MCS (β=0.92, p=.376). Of the background characteristics, high BMI had significant effect on PCS (β=-1.47, p=.015), and age had significant effect on MCS (≤27 years vs. 28-33 years: β=2.71, p=.001). None of the interaction effects were significant on either PCS or MCS. After post hoc Bonferroni adjustment, BMI did not have significant effect.

Table 3
Multivariate mixed model with repeated measures: estimates of main and interaction effects and covariates with 95% Confidence Interval (CI) on the SF-36 Physical Component Scale (PCS) and the Mental component Scale (MCS), N=314.

	PCS			MCS		
Parameter	**Estimate (β)**	**p**	**95% CI**	**Estimate (β)**	**p**	**95% CI**
Intercept	43.38	<.001	40.89 to 45.86	44.53	<.001	41.55 to 47.52
Time						
Baseline	Ref			Ref		
6 Weeks postpartum (6Wpp)	5.84	<.001	3.56 to 8.11	-0.77	.557	-3.35 to 1.80
6 Months postpartum (6Mpp)	10.65	<.001	8.38 to 12.93	1.73	.241	-1.17 to 4.62
Randomization status						
Not randomized	Ref			Ref		
Randomized	-0.62	.493	-2.41 to 1.16	1.09	.320	-1.07 to 3.26
Intervention following ITTa						
Expectant monitoring	Ref			Ref		
Induction of labor	-1.47	.090	-3.16 to 0.23	0.92	.376	-1.13 to 2.97
Age						
≤ 27 years	Ref			Ref		
28 to 33 years	0.98	.141	-0.33 to 2.29	2.71	.001	1.15 to 4.28
≥ 34 years	0.95	.228	-0.60 to 2.50	1.54	.104	-0.32 to 3.39
Parity						
Nulliparous	Ref			Ref		
Multiparous	0.14	.814	-1.01 to 1.28	-1.16	.096	-2.53 to 0.21
Indigenous (Dutch) origin						
Yes	Ref			Ref		
No	-0.41	.642	-2.16 to 1.33	-1.96	.066	-4.04 to 0.13
BMI pre-pregnancy						
< 18.5 (underweight)	-0.73	.542	-2.96 to 1.50	-0.29	.830	-2.94 to 2.36
18.5 to 25 (normal weight)	Ref			Ref		
> 25 (overweight)	-1.47	.015	-2.65 to -0.28	-0.34	.641	-1.76 to 1.08
Educational level						
Lower	Ref			Ref		
Higher	0.75	.270	-0.58 to 2.07	-1.12	.167	-0.47 to 2.70
Interactions						
6Wpp * Randomized	0.53	.719	-2.37 to 3.44	1.63	.330	-1.66 to 4.93
6Mpp * Randomized	-1.32	.372	-4.21 to 1.58	-0.08	.965	-3.77 to 3.61
6Wpp * Induction of labor ITT	1.75	.226	-1.08 to 4.59	-0.20	.904	-3.41 to 3.01
6Mpp * Induction of labor ITT	1.62	.257	-1.19 to 4.44	-0.68	.709	-4.26 to 2.90

a ITT = Intention to treat

Discussion

We investigated the effect of induction of labor compared to expectant monitoring on health-related quality of life (HR-QoL) of women with a intra-uterine growth retardation (IUGR) pregnancy beyond 36 weeks of gestation. We found a difference in self-reported pain at day 4 and day 7 after delivery in favor of induction of labor. However, this difference did not result in HR-QoL differences at six weeks or six months postpartum between the treatments. We did not find any clinically relevant HR-QoL differences between the randomized and non-randomized groups. The physical and mental health as measured with SF-36 were below the Dutch population average at inclusion. The physical health improved over time and was above Dutch population norms at six months postpartum but not above adjusted norm scores for gender and age from the U.S. population. Mental health stayed under the Dutch and U.S. norms.

Maternal HR-QoL has been defined as a secondary outcome to the DIGITAT (Disproportionate Intrauterine Growth Intervention Trial At Term) trial [8-9]. The clinical outcomes of the DIGITAT trial have already shown that induction of labor and expectant monitoring result in equal neonatal and maternal outcomes. Caesarean section rates were also comparable in pregnancies with IUGR beyond 36 weeks of gestation. Other results of the clinical study showed that labor was eventually induced in 49% of the patients in the expectant management arm of the trial, and in the induction arm 5% of the patients had a spontaneous start of the delivery. We have analyzed our HR-QoL data following intention to treat so that our results have captured the effect of initial treatment choice.

Our study has some limitations. First, the patients filled out the questionnaires just once during pregnancy at baseline, regardless of the period between inclusion to the study and childbirth. Therefore, we do not know the short-term impact of waiting, antenatal stress and/or anxiety on HR-QoL during the expectant management period. However, the long-term effect of waiting on HR-QoL was probably small

since the average difference of the waiting period was not more than ten days. Second, we have asked women to report their pain retrospectively, which may not have reflected their real perceived pain but rather their wellbeing during their postpartum period. Further study is needed to gain insight to prospectively self-report of pain after the two treatment strategies. We also don't know how the self-perceived intensity and duration of pain developed between the 7th day and the 6th week after delivery, as we do not have measures between those two time points. Third, we have observed a lower response of non-Dutch women, which may reflect the proportion of women that have difficulties with understanding and/or reading the Dutch or English languages. We have seen that non-indigenous women have somewhat lower HR-QoL scores, which indicates that the total group may have had a lower HR-QoL score. Fourth, prior exclusion of women with illnesses and adverse conditions to the DIGITAT trial may have its obvious impact on mean HR-QoL scores. Our mean HR-QoL scores are therefore not applicable to the total group of women with IUGR. Finally, outcomes of the trial suggest that prior treatment preferences exist: most (80%) of the non-randomized women were monitored expectantly. However, the differences in the randomized and non-randomized groups, which differed in terms of socio-economic status, did not influence responsiveness, or the SF-36 PCS or MCS scores.

An issue that needs further investigation is the fact that average PCS and MCS scores were lower than the population reference norms. The mental health of the DIGITAT patients has been low at all three measurement points. We did not find any systematic effect of educational level, as a proxy of socio-economic status, on the MCS scores. Previous HR-QoL study in women after gestational hypertension or preeclampsia at term randomized for induction of labor or expectant management showed equal to population average MCS scores at six weeks and six months postpartum [22]. This suggests that the findings of the DIGITAT trial are not due to general lower mental health after childbirth. Our findings may, however, have a relation to the mother's concerns, uncertainty or anxiety about the child's health, which is in general suboptimal in the DIGITAT trial as compared to the health of the children from the previous HR-QoL study.

We have presented the results based on the outcomes of the randomized groups. It would also interesting to look at differences in HR-QoL by trial outcomes - e.g. those with cesarean section versus those without, those with a adverse maternal or neonatal outcome versus those without. As we have insufficient statistical power to make such an analysis within DIGITAT data alone, we are planning such an analysis together with HR-QoL data from the HYPITAT study, a similar trial on induction of labor versus expectant management in case of hypertensive disease at term [22].

In summary, in women with IUGR at term, maternal HR-QoL is comparable after induction of labor or expectant monitoring at the long-term. Women report to have had less pain after induction of labor as compared to expectant management in the first week after delivery. In women with a IUGR pregnancy beyond 36 weeks of gestation, induction of labor does not affect maternal quality of life on the long-term.

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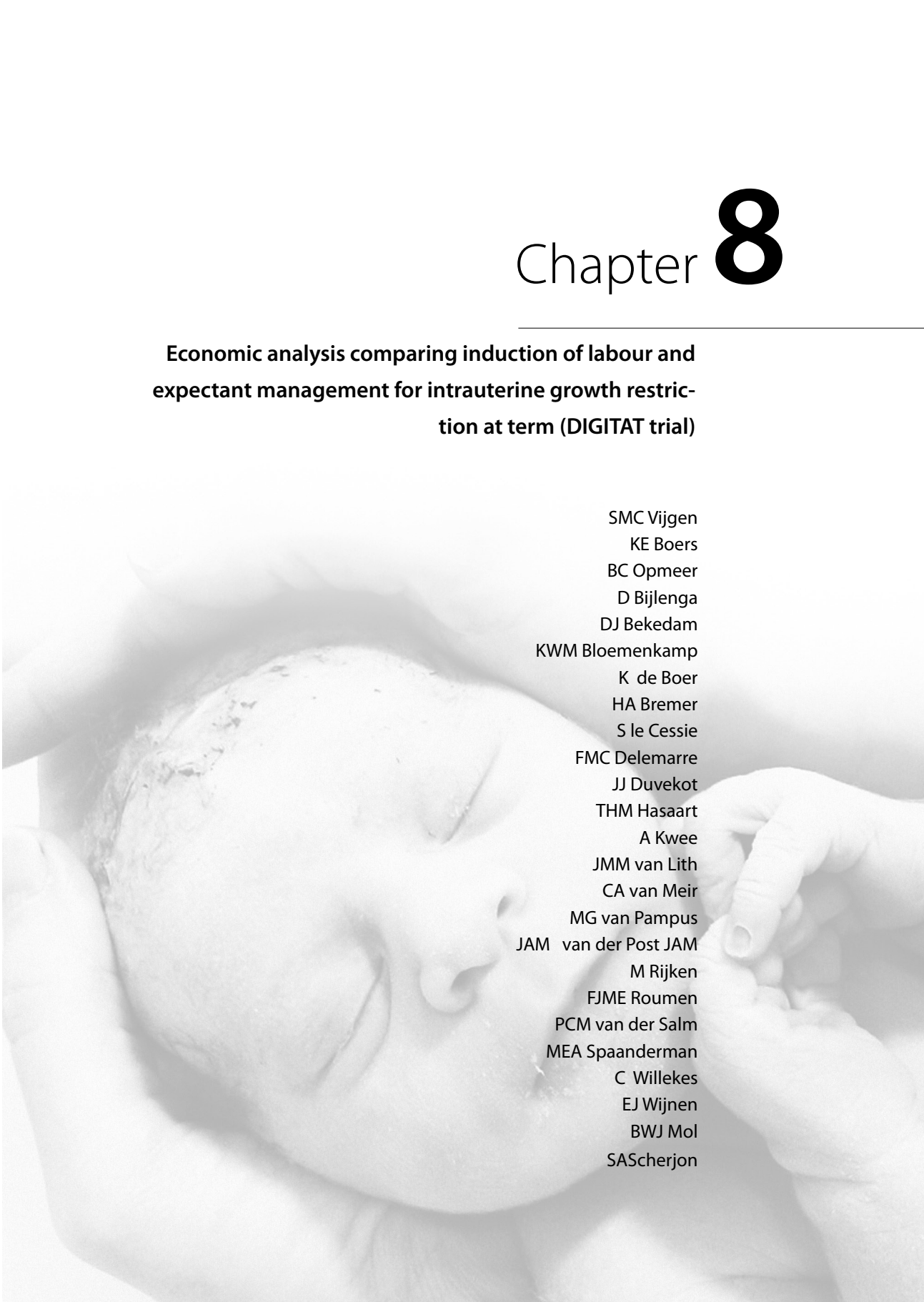
Chapter 8

Economic analysis comparing induction of labour and expectant management for intrauterine growth restriction at term (DIGITAT trial)

SMC Vijgen
KE Boers
BC Opmeer
D Bijlenga
DJ Bekedam
KWM Bloemenkamp
K de Boer
HA Bremer
S le Cessie
FMC Delemarre
JJ Duvekot
THM Hasaart
A Kwee
JMM van Lith
CA van Meir
MG van Pampus
JAM van der Post JAM
M Rijken
FJME Roumen
PCM van der Salm
MEA Spaanderman
C Willekes
EJ Wijnen
BWJ Mol
SAScherjon



Abstract

Objective: Pregnancies complicated by intrauterine growth restriction (IUGR) are at increased risk for neonatal morbidity and mortality. The Dutch nationwide disproportionate intrauterine growth intervention trial at term (DIGITAT trial) showed that induction of labour and expectant monitoring were comparable with respect to composite adverse neonatal outcome and operative delivery. In this study we compare the costs of both strategies.

Study design: A cost analysis was performed alongside the DIGITAT trial, which was a randomised controlled trial in which 650 women with a singleton pregnancy with suspected IUGR beyond 36 weeks of pregnancy were allocated to induction or expectant management. Resource utilization was documented by specific items in the Case Report Forms. Unit costs for clinical resources were calculated from the financial reports of participating hospitals. For primary care costs Dutch standardized prices were used. All costs are presented in Euros converted to the year 2009.

Results: ante partum expectant monitoring generated more costs, mainly due to longer ante partum maternal stays in hospital. For the durante partu and postpartum stage, induction generated more direct medical costs, due to longer stay in the labour room and longer duration of neonatal high care/medium care admissions. From a health care perspective, both strategies generated comparable costs: on average € 7,106 per patient for the induction group (N=321) and € 6,995 for the expectant management group (N=329) with a cost difference of € 111 (95%CI: - € 1,296 to € 1,641).

Conclusion: In women with pregnancies complicated by IUGR at term, induction of labour generates identical health care costs as compared to expectant management.

Introduction

Intrauterine growth restriction (IUGR) at term is a major problem for obstetricians in clinical practice, because it is associated with increased neonatal mortality and short and long term neonatal morbidity.[1-5] At present there is no consensus among obstetricians on what policy to follow in pregnancies with suspected fetal growth restriction at term. Induction of labour might increase the risk of instrumental deliveries and caesarean sections, and therefore increase maternal and neonatal morbidity as well as costs. Expectant management on the other hand might increase the risk of perinatal complications, including stillbirth.
Since evidence on this point was lacking, we recently performed a randomised clinical trial on the subject, named the Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT, number ISRCTN10363217).[6] In this 650 patient study, the composite adverse neonatal outcomes and caesarean sections were comparable in both groups.[7]

In the expected group babies were delivered on average 10 days later and weighted 130 grams more as compared to the induction group. Overall, in women with suspected IUGR at term no important differences were found between induction of labour and expectant monitoring concerning immediate adverse neonatal outcome or operative delivery rate. However, significantly more neonates from the induction group were admitted to high or medium levels of care.[7] It is unclear whether these strategies differ in terms of costs generated by health care utilisation. At present, evidence on costs and cost-effectiveness of management of women with suspected IUGR at term is limited.

This study reports the economic evaluation that we performed alongside the DIGITAT trial, in which induction of labour and expectant monitoring were compared in pregnancies complicated by suspected intrauterine growth restriction beyond 36 weeks of gestation.

Methods

Trial design

Full details of the DIGITAT trial were reported previously.[6] The trial was approved by the Institutional Review Board of the University of Leiden and had local approval from Boards of the other participating hospitals. The trial has been registered in the clinical trial register as ISRCTN10363217.

In short, the study was a multicentre randomised controlled clinical trial in obstetric departments of 8 academic and 44 non-academic hospitals in The Netherlands. Women diagnosed with suspected IUGR beyond 36 weeks of pregnancy with a singleton fetus in cephalic presentation were allocated to either induction of labour or expectant monitoring. Suspected IUGR was defined as a fetal abdominal circumference (FAC) below the 10th percentile, or an estimated fetal weight (EFW) below the 10th percentile, or a flattening of the FAC curve by ultrasound.

In the induction group, labour was induced within 48 hours after randomization, according to local protocol. In the expectant group, patients were monitored by local protocol until the onset of spontaneous delivery with daily fetal movement counts, and at least twice weekly heart rate tracings and weekly ultrasound examination. If there were signs of sub-optimality in any of these recordings induction of labour was the treatment of choice. Maternal monitoring consisted of frequent blood pressure measurements, assessment of proteïnuria and laboratory tests of liver and kidney function and full blood count all at the discretion of the attending obstetricians. Monitoring could take place in an outpatient setting or during admission to the hospital.

All patients who declined randomisation, but who gave authorization for the use of their medical data were registered as non-participants. Identical data were collected prospectively and entered into the trial database. The primary outcome in this trial was a composite measure of adverse neonatal outcome, defined as death before hospital discharge, 5-minute Apgar score < 7, umbilical artery pH < 7.05, or admission to the neonatal intensive care.

Analysis of the clinical endpoints showed comparable neonatal outcomes between both groups, the prevalence of composite adverse neonatal outcome was 17 (5.3%) for the induction group versus 20 (6.1%) in the expectant monitoring group; difference – 0.8% (95% CI – 4,3% to 3.2%). There was no perinatal mortality in the trial. The number of caesarean sections (respectively 45 (14,0%) versus 45 (13.7%); difference 0.3% (95% CI -5.0% to 5.6%)) were comparable as well.[7]

Economic evaluation

A cost analysis was performed alongside the trial. We used a health care perspective, in which only medical costs are included, with a time horizon until hospital discharge. Thereby, by documenting details on utilisation of health care resources, we provide insight in the clinical origins of costs associated with management of these high-risk pregnancies.

As both strategies were comparable in terms of health outcomes, we performed a cost-minimization analysis in which only the costs of both strategies were compared.[8] We differentiated three phases of the clinical process in which costs arise: ante partum costs (from the moment of randomisation until childbirth), costs related to the delivery, and postpartum costs (from the moment of childbirth until hospital discharge). No discounting was applied because all costs occurred within one year.

Resource utilisation

Resource use during the admission period was documented in the Case Report Form (CRF). The following resource items were collected: maternal and neonatal admissions, method of delivery, outpatient visits, medication, maternal laboratory tests, cardiotocograms (CTGs) and fetal ultrasounds. Maternal admissions were differentiated into three levels of care (intensive, medium, or ward). Neonatal admissions were divided into four levels of care (intensive, high, medium, or ward). Neonatal admissions on maternal ward were not included in our analyses because we assumed these were already included in the maternal ward costs.

As induction of labour takes place inside the labour room, we expected that stays

in the labour room will be longer in the induction group due to time needed for induction. This difference was accounted for by measuring use of the labour room as hours between admission to labour room and birth plus one hour extra for extended recovery care, and estimated unit costs associated with one hour of labour room use. In case a caesarean section was performed, use of the operation room (in hours) was estimated as well.

Unit costs

Unit cost estimates were based on several sources: top-down calculations provided by the financial departments in one participating academic and one participating general hospital (for maternal and neonatal admissions to ward, medical care, obstetric high care, (N)ICU and neonatal monitoring), bottom-up calculation (one hour use of the labour room and operating theatre), Dutch standardized prices (visits to primary and paramedical health care providers and outpatient visits), and market prices (medication).[9-10] In Table 1 unit costs together with valuation methods and sources are presented. All unit costs were expressed in 2009 Euros using the consumer pricing index.[11]

Analyses

Group differences in resource use were tested by using the nonparametric Mann-Whitney U test, because such data are generally not normally distributed. Resource use per patient was multiplied by unit costs, and total costs per patient were estimated. Mean total costs per patient as well as median costs were estimated, and differences in total costs between study groups are tested using the nonparametric Mann-Whitney test. Differences in mean costs and 95% confidence intervals were determined by bootstrapping. Statistical and simulation analyses were performed using SPSS software (version 16.0) and Microsoft Excel.

Table 1
Cost-analyses: units of resource use, unit costs, valuation method and volume source

	Unit	Unit cost	Valuation method (source)	Volume source
Medical costs				
*Admission mother**				
hospital stay - ward	Day	359	top-down calculation	CRF
hospital stay - medium care	Day	546	top-down calculation	CRF
hospital-stay - intensive care	Day	1742	top-down calculation	CRF
*Admission child**				
hospital stay - medium care	Day	546	top-down calculation	CRF
hospital stay - high care	Day	1462	top-down calculation	CRF
hospital-stay - NICU	Day	1514	top-down calculation	CRF
specialist care	Hour	72	Dutch costing guidelines	CRF/AQ
outpatient visit*	Visit	85	top-down calculation	CRF/AQ
psychologist	Hour	35	Dutch costing guidelines	AQ
midwife	Hour	35	Dutch costing guidelines	AQ
general practitioner	Visit	22	Dutch costing guidelines	AQ
paramedical	Visit	25	Dutch costing guidelines	AQ
home care	Hour	33	Dutch costing guidelines	AQ
Induction methods#	Gift	16	Pharmacotherapeutic website	CRF
Medication#	dose per day	7	Pharmacotherapeutic website	CRF
Analgesics during labour#	procedure	167	top-down calculation	CRF
Neonatal monitoring#	procedure	93	top-down calculation	CRF
Operation room*	Hour	145	bottom-up calculation	CRF
Labour room*	Hour	85	bottom-up calculation	CRF
Non-medical costs				
Travel costs- car	Km	0.18	Dutch costing guidelines	AQ
Travel costs- public transport	km	0.18	Dutch costing guidelines	AQ
Informal care	Hour	9.10	Dutch costing guidelines	AQ
Productivity loss	Hour	27	Dutch costing guidelines	AQ

* the mean of the unit cost for an academic hospital and for a general hospital is presented
CRF= Case Report Form
AQ= additional questionaire
# the mean of several methods/medications is presented

Results

Between November 2004 and November 2008, we approached 1.116 women, of whom 650 were randomised to induction (n = 321) or expectant management (n = 329), 452 declined randomisation and 14 refused any use of identifiable data.

Average volumes of resource utilization, total costs in each study group as well as average costs per patient are presented in Table 2. During the ante partum phase from moment of randomisation until start of delivery, maternal admissions were compared to the induction group longer in the expectant monitoring group, respectievely 2.8 versus 8.2 days for medium care (p=< 0.05) and 2.2 versus 4.7 days on maternal ward (p<0.001). More outpatient CTGs (2.1 versus 4.8, p<0.001), more ultrasounds (1,3 versus 2,1, p<0.001), more scheduled outpatient visits (1.9 versus 4.4, p<0.001), more unscheduled outpatient visits (1.3 versus 1.6, p<0.001) and more maternal assessments (5.4 versus 9.9, p<0.001) occurred in the expectant monitoring group. Admission because of labour was somewhat longer in the induction group (1.8 days versus 1.4 days, p<0.001).
The duration of admission in the labour room and/ or operating theatre was also longer for the induced patients in case of spontaneous delivery (15.4 versus 8.3 hours, p<0.001), in case of vacuum or forcipal extractions (25 versus 11 hours, p<0.05) and in caesarean deliveries (18.3 versus 11.9 hours, p<0.05). From childbirth until hospital discharge no significant differences appeared in the duration of maternal and neonatal admissions. However, as can be seen from table 2 more neonates in the induction group were admitted to medium care wards compared to the expectant monitoring group (44% versus 31%).

Table 2
:Resource use, mean costs per patient and total costs, randomised patients (2009 Euros)

		Induction (N=321)				Expectant management (N=329)				
	Unit	% patients using care	Mean volume*	Total Costs	Mean Costs pp	% patients using care	Mean volume*	Total Costs	Mean Costs pp	Difference (I-EM)
Maternal admission MC	days	3%	2.8	12198	38	4%	8.2	40138	122	-84
Maternal admission ward	days	24%	2.2	54891	171	33%	4.7	162526	494	-323
Home care	days	3%	6.5	2247	7	8%	8.7	7238	22	-15
Outpatient CTGs	procedure	20%	2.1	4173	13	72%	4.8	34216	104	-91
CTGs during admission	procedure	98%	4.6	43335	135	97%	7.0	66787	203	-68
Ultrasounds	procedure	12%	1.3	1284	4	66%	2.1	13818	42	-38
Scheduled outpatient visits	visit	21%	1.9	10593	33	72%	4.4	89817	273	-240
Unscheduled outpatiet visits	visit	4%	1.3	1284	4	26%	1.6	11515	35	-31
Maternal assessments	procedure	83%	5.4	11556	36	97%	9.9	25004	76	-40
Medication#				32,1	0,1			329	1	-0,9
Laboratorium tests	test	67%	1.6	642	2	61%	1.7	658	2	0
Total ante partum				142235,1	443			452046	1374	-931
Admission because of labour	day	90%	1.8	175587	547	86%	1.4	136864	416	131
Induction PGE gel	Gift	52%	1.9	13482	42	20%	1.8	4935	15	27
Induction PGE tablets	Gift	8%	3.0	288,9	0,9	7%	2.1	197,4	0,6	0,3
Amniotomy and oxytocin	procedure	24%	-	64,2	0,2	18%	-	65,8	0,2	0
Medication during labour#	Unit	51%	-	24396	76	42%	-	21056	64	12
Spontaneous route of delivery	hours	78%	15.4	322605	1005	78%	8.3	179963	547	458
Instrumentel delivery	hours	8%	25.0	57138	178	8%	11.1	25662	78	100
Caesarean delivery	hours	14%	18.3	71904	224	14%	11.9	47376	144	80
Episiotomy	procedure	21%	-	1284	4	28%	-	1645	5	-1
Total delivery				666749,1	2077			417764	1270	807
Maternal admission IC	days	1%	6.0	0	49	1%	5.0	13160	40	9
Maternal admission MC	days	1%	3.5	5457	17	2%	4.1	12502	38	-21
Maternal admission ward	days	63%	4.1	277665	865	63%	3.9	272083	827	38
Maternal homecare	days	9%	4.3	4173	13	10%	3.7	3948	12	1
Neonatal admission IC	days	3%	6.4	88275	275	4%	13.1	257936	784	-509
Neonatal admission HC	days	8%	14.5	511674	1594	8%	11.0	426055	1295	299
Neonatal admission MC	days	44%	8.5	549552	1712	31%	9.5	423752	1288	424
Consult paediatrician	visit	71%	1.1	17976	56	65%	1.1	17108	52	4
Neonatal monitoring	procedure	7%	-	1605	5	10%	-	4935	15	-10
Total postpartum				1456377	4586			1418319	4351	235
Total costs					7106				6995	111

* of patients using care # medication costs are an summation of several medications, therefore no unit and mean volume is given

A summary of the mean and median costs per patient is provided in Table 3. In the ante partum period mean costs per patient appeared to be higher in the expectant monitoring group (difference - €931). On the other hand, during delivery induction of labour generated more costs than expectant management (difference €807), mainly because induction required a longer stay labour room and/ or operating theatre.

In the postpartum period, women in the induction group also generated more costs than women monitored expectantly (difference: €235).

Overall, mean costs per patient were €7.106 for induction and €6.995 in the expectant monitoring group (difference €111: 95% CI -1295 to 1640).

Table 3
Comparison of costs between randomised induction of labour and expectant management

	Induction (N=321)	**Expectant management (N=329)**	**Differential mean cost***		
	Mean	Median (IQR)	Mean	Median (IQR)	(95% CI)#
Total ante partum	443	218 (110-573)	1374	824 (485-1694)	
-931					
Total delivery	2077	1399 (916-2785)	1270	949 (635-1478)	807
Total postpartum	4586	1941 (596-5136)	4351	1264 (138-4271)	235
Total costs	7106	4680 (2296-8610)	6995	3954 (2164-7569)	111(-1296- 1641)

*Induction minus expectant management
non-parametric confidence interval based on 1000 bootstrap replications

Discussion

In this study we estimated the costs of pregnant women with a diagnosis of IUGR at term in whom labour was induced and those who were monitored expectantly using the data of the DIGITAT trial. The trial did not detect differences in maternal or neonatal outcomes or in operative delivery rates, so the economic evaluation was set up as a cost-minimization analysis. We found comparable costs after induction of labour and expectant management in women with suspected intrauterine growth restriction at term. Within a study horizon from moment of randomisation until postpartum hospital discharge induction of labour and expectant management resulted in comparable medical costs per patient. Unsurprisingly, the distribution of costs over the different phases in each strategy shows higher ante partum costs (due to longer maternal admissions) in the expectant group and higher delivery costs (due to the induction itself) in the induction group. Costs due to postpartum maternal and neonatal admissions are comparable between both groups.

This adds to equivalent fetal and maternal outcomes as well as quality of life[12], indicating that both approaches are both acceptable management strategies. If a policy of induction for near term growth restriction is to be followed, deferring induction until 38 weeks, while strictly monitoring mother and child, may prevent complications of late prematurity and neonatal admissions.[13] However, beyond 38 weeks, there is not much to win by further postponing delivery, neither in medical outcomes, and probably nor in costs.

To our knowledge this is the first economic evaluation that prospectively compared these strategies in this patient population. We used trial-based data that were collected prospectively.

In earlier studies we reported comparable neonatal and maternal outcomes after labour induction and expectant management in at term IUGR.[7] The same applies to more detailed neonatal morbidity.[13] A quality of life study alongside the DIGI-

TAT trial was performed by Bijlenga et al. on behalf of the DIGITAT study group. In this study health related quality of life was measured in 361 randomised women, 6 weeks and 6 months after childbirth using validated questionnaires. From the results it could be concluded that in pregnancies complicated by IUGR beyond 36 weeks, induction of labour does not affect the long-term maternal quality of life. [12]
The equipoise in antenatal and postnatal costs in the DIGITAT trial was not found in the cost-analysis of a comparable RCT, that compared induction to expectant management in women with gestational hypertension or mild pre-eclampsia at term.[14-15] In this study induction of labour was less costly than expectant monitoring because of differences in resource use in the ante partum period.[15]
Because more than 50 hospitals from all over the Netherlands, teaching as well as non-teaching, participated to the DIGITAT trial the study population was representative for Dutch population. However, women who declined randomisation were older, slimmer, higher educated and smoked less.7,[16] In a comparison between participants and non-participants, we found a trend towards worse neonatal outcomes and higher operative delivery rates among non-participants. Probably this finding would translate into higher costs in this group, even though they had higher SES.[16]

Our analysis focused on short term and a with a health care perspective. The advantage of that is the use of direct clinical trial data for both costs and effects.

We also tried to study longer term and societal costs as well by analyzing questionnaires filled out by a very small subsample of the study population (n=27). After including these costs, induction of labour became significantly more expensive than expectant monitoring. However, because of the unreliability of the follow-up data in this economic analysis we decided to focus on the short-term medical costs. Because growth restriction is associated with a less favourable (neuro)developmental outcome, we also investigated the outcome of children randomised during DIGITAT after two years.[17] As that follow-up indicated no differences in child behaviour at 2 years between induction and expectant management, we think it is not necessary

to include long term and societal costs for the children in our economic analysis. Strengths of our study are the use of trial-based data for the economic analysis, and exactly the same patients were studied as for the clinical analysis. Transferring the data to the general patient population is valid because of the large number and diversity of the participating hospitals.

With this study we further aimed to define the best strategy in at term IUGR by analysing costs generated by induction compared to expectant management, since primary neonatal and delivery outcomes, as well as more detailed neonatal morbidity and maternal quality of life were comparable between the two strategies. The antenatal costs of expectant management in IUGR were higher due to higher consumption of medical care by monitoring mother and child. However, induction group babies had a higher medical consumption after birth, mainly due to neonatal hospital admissions in exchange. In order to do defer delivery in IUGR, both mother and child were strictly monitored, until either labour was induced because of fetal or maternal deterioration or spontaneous delivery started. As expected, this imposed higher resource use antenatal. On the contrary, more children were admitted to intermediate levels of care after induction, mainly due to lower gestational age and related birth weight at delivery[12], accounting for higher resource use after birth. Since costs are not higher after expectant management, postponing delivery beyond 38 weeks gestation for as long as neonatal condition is reassuring is reasonable, providing monitoring of mother and child. By this means, the number of neonatal admissions can be restricted. We plan to analyse whether this approach will generate less costs.

Induction of labour and expectant monitoring in at term IUGR have comparable outcomes immediately after birth in terms of obstetrical outcomes, maternal quality of life and costs. Providing strict monitoring of mother and child induction of labour is reasonable to pre-empt possible stillbirth in suspected IUGR, if feasible after 38 weeks gestation.

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Chapter 9

Effects on (neuro)developmental and behavioral outcome at 2 years of age of induced labor compared with expectant management in intrauterine growth restricted infants - long term outcomes of the DIGITAT-trial.

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KE Boers
JAM van der Post
MG van Pampus
AG van Wassenaer
AL van Baar
MEA Spaanderdam
JH Becker
A Kwee
JJ Duvekot
HA Bremer
FMC Delemarre
KWM Bloemenkamp KWM
CJM de Groot CJM
C Willekes
FJME Roumen
LMM van Lith
BMJ Mol
S le Cessie
SA Scherjon

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Abstract

Objective: To study long term (neuro)developmental and behavioral outcome of pregnancies complicated by intrauterine growth restriction at term in relation to induction of labor or an expectant management.

Methods: Parents of 2-year old children included in the DIGITAT-trial answered the Ages and Stages Questionnaire (ASQ) and Child Behaviour Check List (CBCL).

Results: We approached 582 (89.5%) of 650 parents. The response rate was 50%. Of these children, 27% had an abnormal score on the ASQ and 13 % on the CBCL. Results of the ASQ and the CBCL for the two policies were comparable. Low birth weight, positive morbidity assessment index (MAIN score) and admission to intermediate care, increased the risk of an abnormal outcome of the ASQ. This effect was not seen for the CBCL.

Conclusion: In women with IUGR at term, both a policy of induction of labor and expectant management do not affect developmental and behavioral outcome when compared to expectant management.

Key words: DIGITAT-trial, intrauterine growth restriction, long-term outcome, Ages and Stages Questionnaire, Child Behaviour Checklist.

Introduction

Intrauterine growth restriction at term is associated with increased perinatal morbidity and mortality[1-7]. Long-term morbidity is also increased in pregnancies complicated by IUGR. Studies have reported learning difficulties, defects in speech, neurological deficits and behavioral problems to occur more frequently in term neonates born small for gestational age (SGA) [8-17].

The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT) compared the effect of induction of labor in pregnancies complicated by IUGR with an expectant monitoring policy[18]. The results of this study showed no important differences in adverse neonatal outcome between the two randomized groups. However, in de induction group, more neonates were admitted to intermediate care after induction than neonates in the expectant monitoring group (48% v. 36%). After a policy of expectant management, a larger percentage of neonates were born with a birth weight below the 10th centile when compared to neonates in the induction group (13% v. 31%, mean difference -18% [95% CI: 12% to 24%]). In both groups, neonatal admissions as well as MAIN score (morbidity assessment index for newborns) were lower beyond 38 weeks gestational age. [18-19-20].

The objectives of this study were to[1] study the long-term effects on (neuro)developmental and behavioral outcome of pregnancies complicated by intrauterine growth restriction at term and to [2] compare the influence of induction of labor to an expectant management policy on these long-term outcomes.

Methods

Participants

The study population consisted of children born to mothers who participated in the DIGTAT-trial. Between November 2004 and November 2008, pregnant women

with a singleton fetus in cephalic presentation, and suspected IUGR between 36+0 and 41+0 weeks were recruited. Suspected IUGR was defined as a fetal abdominal circumference (AC) or an estimated fetal weight (EFW) below the 10th percentile, or deceleration of the fetal abdominal circumference growth in the third trimester. Consenting women were randomly allocated to either induction or expectant monitoring. Participants allocated to the expectant monitoring group were strictly monitored until the onset of spontaneous labor. Details of the DIGITAT trial have been described elsewhere[18].

Baseline and neonatal characteristics

Data such as maternal characteristics around the time of randomization, gestational age at birth, birth weight, composite adverse neonatal outcome and MAIN score were recorded in the original trial. Composite adverse neonatal outcome was defined as neonatal death, five minute Apgar score <7, umbilical artery pH < 7.05 or admission to neonatal intensive care. The MAIN score is a validated numeric index outcome of early neonatal outcomes of prenatal care and adverse prenatal exposures in babies delivered beyond 28 weeks gestational age and was calculated for all the neonates based on the characteristics recorded around birth. A MAIN score greater than zero indicates the presence of neonatal morbidity (ranging from mild to severe morbidity)[19;20].

Developmental assessment: The Ages and Stages Questionnaire

The Ages and Stages Questionnaire (ASQ)21 is a screening questionnaire designed to detect developmental delay in children. It contains questions to be answered by parents about five areas of development of their child: communication, gross motor, fine motor, problem solving and personal-social. For each area, a mean score is calculated. The higher the score, the more abnormal the outcome is. An abnormal score is a score of two standard deviations or more below the expected mean of a reference population, adjusted for age, and indicates a delay in development and a need for further assessment.

The Child Behaviour Checklist

The Child Behavior Checklist (CBCL)22 consists of 100 items concerning behavioral problems, on the basis of which a Total Problem score can be computed. It also informs on 7 narrow band syndrome scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behavior), and two broad-band scales (internalizing and externalizing behavior). For each scale a standardized T-score is calculated and a score > the 97th percentile falls into the clinical range that indicates serious behavior problems. The higher the T-score, the more serious the behavioral problems are.

Procedure

Parents of children randomized in the DIGITAT-trial (n=650) were requested to fill out the two questionnaires about the development of their child when their child was between 23 and 26 months of age. Research nurses contacted the parents by phone and subsequently sent out the questionnaires by post. If the parents had not responded to the questionnaires, they were contacted again by the research nurses.

Statistical analysis

The number of children with abnormal scores for the ASQ and the CBCL were compared for the two groups with a policy of induction of labor or expectant management using the chi-squared test. For both questionnaires, the mean scores per area were compared between the two groups using t-tests. Univariate analyses were performed using chi-square for categorical values or t-tests for means to identify factors of influence on the ASQ and CBCL by comparing children with an abnormal outcome to those without developmental problems. Factors with a p-value below 0.10 were entered in a logistical regression model, either as continuous or as categorical variables, to assess the joint influence on the outcome of the ASQ and CBCL test. SPSS version 16.0 (IBM, Chicago, IL) was used.

Results

Of the 650 parents of children, 582 (89.5%) randomized in the original trial were approached (Figure 1). Two parents were not approached because their children were born with serious congenital abnormalities are caregivers of another child were not approached as the mother died post-partum of unknown causes. The response rate within the approached group was 54% (n=158) in the induction group and 46% (n=133) in the expectant monitoring group (p = 0.02). In both groups, a small number (n=24) of questionnaires were discarded because they were incomplete or filled in when the child was younger than 23 or older than 26 months.

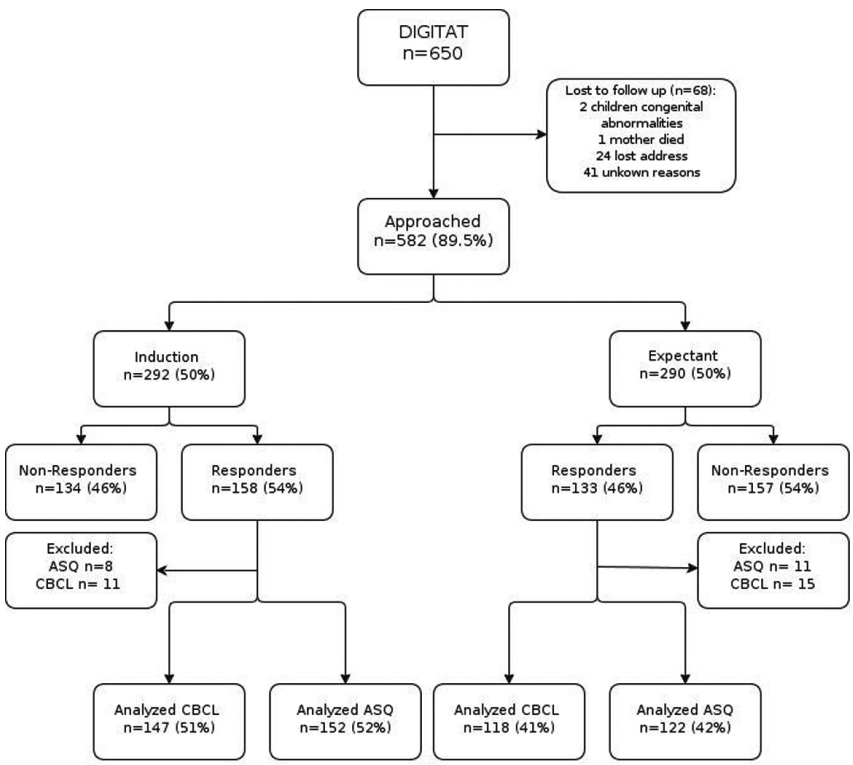

Table 1
Baseline characteristics

Characteristic	Approached (n=582)	Non-approached (n=68)	Difference in % or mean (95% CI)	Respondents (n=292)	Non-respondents (n=290)	Difference in % or mean (95% CI)	Induction of labor (n=158)	Expectant Management (n=134)	Difference in % or mean (95% CI)
	A	B	A-B	C	D	C-D	E	F	E-F
Maternal age (years)	27.2 (23.4-31.3)	24.9 (21.7-30.5)	1.0 (-0.3; 2.4)	28.1 (25.1-31.9)	26.2 (22.2-30.6)	1.8 (1.0; 2.6)**	28.0 (25.1-32.1)	28.2 (24.7-31.5)	-0.1 (-1.3; 0.9)
BMI at study entry†	22.1 (19.7-25.5)	22.1 (19.6-25.5)	-0.4 (-1.7; 1.0)	22.1 (19.9-25.7)	22.0 (19.4-25.4)	0.1 (-0.7; 0.9)	22.1 (19.9-25.8)	23.2 (20.2-25.3)	0 (-1.2; 1.2)
Maternal smoking§	229 (39.3)	36 (52.9)	-13.6 (-26.1; -1.1)*	96 (32.9)	133 (45.9)	-13.0 (-20.9; -5.1)**	53 (33.5)	43 (32.1)	-1.4 (-9.3; 12.2)
Caucasian‡	451 (77.5)	56 (82.4)	-4.9 (-14.5; 14.3)	253 (86.6)	198 (68.3)	18.4 (11.7; 24.9)**	139 (88.0)	114 (85.1)	2.9 (-4.9; 10.8)
Education									
Lower professional school	303 (52.1)	35 (51.5)	0.6 (-11.9; 13.1)	147 (50.3)	156 (53.8)	-3.5 (-11.6; 4.6)	83 (52.5)	64 (47.8)	4.8 (-6.7; 16.3)
Higher professional school	58 (10.0)	5 (7.4)	2.6 (-4.0; 9.3)	35 (12.0)	23 (7.9)	4.1 (-0.8; 8.9)	16 (10.1)	19 (14.2)	-4.1 (-11.6; 3.5)
Gestational age at birth (days)	270.5 (263.2-278.7)	268.9 (263.8-279.8)	0.2 (-2.3; 2.7)	269.9 (263.9-278.7)	271.5 (262.9-278.9)	-0.3 (-1.8; 1.2)	266.4 (261.5-271.2)	277.5 (269.8-283.6)	-9.9 (-11.8; -7.9)
Birth weight (grams)	2485.0 (2233.8-2750.0)	2487.5 (2250.0-2911.3)	-17.8 (-115.2; 79.5)	2490.0 (2215.0-2755.0)	2482.5 (2259.0-2745.0)	-23.7 (-83.5; 36.2)	2435.0 (2173.8-2660.0)	2600.0 (2230.0-2850.0	-133.8 (-221.2; -46.5) **
Birth weight below the 10th centile	407 (69.9)	44 (64.7)	5.2 (-6.7; 17.2)	205 (70.0%)	202 (69.8)	0.5 (-6.9; 8.0)	103 (65.2)	102 (76.1)	-10.9 (-21.3; -0.6)*
Intermediate level of care admission	245 (42.1)	30 (44.1)	-2.0 (-14.5; 10.4)	130 (44.5)	115 (39.7)	4.8 (-3.1; 12.9)	77 (48.7)	53 (39.6)	9.1 (-2.2; 20.6)
MAIN score > zero	128 (22.0)	17 (25.0)	-3.0 (-13.8; 7.8)	69 (23.6)	59 (20.3)	3.3 (-3.4; 10.0)	40 (25.3)	29 (21.6)	3.7 (-6.1; 13.4)
Composite adverse neonatal outcome	29 (5.0)	8 (11.8)	-6.7 (-14.6; 1.0)	14 (4.8)	15 (5.2)	-0.4 (-3.9; 3.2)	7 (4.4)	7 (5.2)	-0.8 (-5.7; 4.2)
Randomization									
Induction	292 (50.2)	30 (44.1)	5.9 (-6.6; 18.4)	158 (54.1)	133 (45.9)	8.2 (0.15; 16.3)*	NA	NA	NA
Expectant Management	290 (49.8)	38 (55.9)	-5.8 (-18.4; 6.6)	134 (45.9)	157 (54.1)	-8.2 (-16.3; -0.15)*	NA	NA	NA

** p < 0·001, * p<0·05
Table shows median (interquartil25th to 75th percentile or number (%)).
Data were compared between respondents and non-respondents with the Student t-test, chi-square or fisher exact test.
†n=506 for approached; n= 61 for non-approached; n=263 for respondents; n=246 for non-respondents n=141 for induction; n=122 for expectant
§n=535 for approached; n= 66 for non-approached; n=267 for respondents; n=272 for non-respondents n=144 for induction; n=123 for expectant
‡n=545 for approached; n=67 for non-approached; n=278 for respondents; n=271 for non-respondents n=151 for induction; n=127 for expectant

Baseline characteristics

The baseline characteristics of the two management groups, as well as of the non-respondents and non-approached participants are shown in table 1. Similar to the findings of the primary trial, children in the induction group are lighter at birth with a lower gestational age than children in the expectant management group. Baseline characteristics of the respondents were also compared with the non-respondents/non-approached. The responding mothers were older, less likely to smoke and more frequently Caucasian than the non-respondents. When comparing the approached group to the non-approached group, we found that women in the non-approached group were more likely to smoke.

Ages and Stages Questionnaire

For the Ages and Stages questionnaire, 25% (n=38) of the children in the induction group and 29% (n=35) of the children in the expectant management group had an abnormal score in one or more areas of development (Table 2). The mean scores per problem area were calculated for induction and expectant management. No significant differences were found in the mean scores (Table 3) or in the number of children with abnormal scores (Table 2) between a policy of induction compared to expectant management.

Table 2
Number of children with abnormal scores of the ASQ or CBCL in one or more areas.

Questionnaire	Induction of labor n (%)†	Expectant Management n (%)§	Difference in percentage (95% CI)
Ages and Stages	38 (25)	35 (29)	-4 (-14; 7)
CBCL	21 (14)	13 (11)	3 (-5, 11)
†n= 152 for ASQ; n=147 for CBCL			
§n=122 for ASQ; n=118 for CBCL			

Table 2
Mean scores for the ASQ and CBCL compared between the two groups.

Problem Area ASQ	Induction	Expectant Management	
	ASQ (n=152)	**ASQ (n=122)**	**p-value**
Communication	50.9 (11.7)	51.2 (13.1)	0.8
Gross Motor	53.7 (13.4)	52.3 (10.2)	0.3
Fine Motor	48.7 (9.3)	47.9 (11.2)	0.5
Problem Solving	42.3 (10.4)	44.1 (12.5)	0.2
Personal Social	46.7 (11.0)	47.3 (11.6)	0.7
Syndrome Scale CBCL	**CBCL (n=122)**	**CBCL (n=118)**	**p-value**
Emotionally Reactive	52.9 (5)	52.6 (4.5)	0.6
Anxious/Depressed	51.3 (2.9)	50.9 (2.0)	0.2
Somatic complaints	54.3 (7.1)	54.1 (6.3)	0.8
Withdrawn	53.0 (5.4)	52.3 (4.0)	0.2
Sleep problems	53.0 (5.9)	52.2 (5.5)	0.3
Attention problems	54.1 (5.2)	53.7 (5.0)	0.5
Aggressive behavior	53.9 (5.9)	53.4 (4.9)	0.5
Internalizing	45.5 (10.7)	44.7 (9.2)	0.5
Externalizing	50.2 (9.2)	48.2 (9.9)	0.1
Total problem score	47.6 (9.9)	45.6 (9.8)	0.1

Table shows mean score per area (ASQ) or mean T-score (CBCL) and standard deviation.
Groups were compared using the Student t-test.

Child Behaviour Checklist

For the CBCL, 14% in the induction group and 11% in the expectant management group had an abnormal score in one or more areas of the CBCL (Table 2). There were no differences between the mean T-scores between a policy of induction of labor compared to expectant management (Table 3).

Table 4 shows that 43% of children with a birth weight below the 2.3rd centile had an abnormal outcome of the ASQ, and that lower percentages with abnormal scores were found in higher birth weight centiles ($p<0.001$). 35% of children with a MAIN score greater than zero had an abnormal outcome of the ASQ compared to 22% of children with a MAIN score equal to zero ($p=0.04$). None of the four children admitted to the intensive care had a poor outcome of the ASQ. However, of the children admitted to an intermediate level of care, 34% had an abnormal outcome

of the ASQ, significantly higher than the 20% abnormal scores found in children not admitted or admitted to the maternal ward (p=0.005). No significant correlation was found between gestational age at birth, composite adverse neonatal outcome at birth, management policy, maternal smoking during pregnancy or education level of mother and an abnormal outcome of the ASQ. We could not identify any

Table 4
Univariate analysis of possible factors of influence on the ASQ or CBCL

	Any abnormal ASQ domain	P-value	Any abnormal CBCL domain	P-value
Birth weight centiles				
<p 2.3	22 (43%)	p<0.001	9 (18 %)	0.3*
p2.3 – p5	20 (29%)	p=0.01	5 (8%)	
p5 – p10	20 (29%)	p=0.01	7 (11%)	
>p10	11 (13%)	reference	13 (16%)	
Gestational Age (weeks)				
36 – 36+6	12 (36%)	0.6*		0.4*
37 – 37+6	12 (19%)		6 (10%)	
38 – 38+6	20 (29%)		12 (17%)	
39 – 39+6	12 (25%)		6 (13%)	
40 – 40+6	13 (30%)		2 (5%)	
41+	4 (21%)		2 (11%)	
Composite adverse neonatal outcome at birth				
Yes	1 (7.7%)	0.1	2 (17%)	0.9
No	72 (27.6%)		22 (14%)	
MAIN score > zero				
Yes	23 (35%)	0.04	9 (14%)	0.7
No	44 (22%)		24 (13%)	
Admission type after birth				
Intensive Care	0 (0%)	0.14	1 (33%)	0.1*
Intermediate level of care	41 (34.2%)	0.005	15 (13%)	
Maternal Ward/No admission	30 (20%)	reference	17 (12%)	
Management Policy				
Induction	38 (25%)	0.5	21 (14%)	0.4
Expectant Management	35 (29%)		13 (11%)	
Maternal smoking during pregnancy				
Yes	22 (25%)	0.7	12 (14%)	0.9
No	45 (27.4%)		22 (14%)	
Education of mother				
Lower professional school	39 (29%)	0.09	15 (11%)	0.3
Higher professional school	5 (14.7%)		2 (6%)	

Percentages were compared between normal and abnormal scores using chi-square.
* No significant differences between subgroups.

factors which were significantly related to the outcome of the CBCL (Table 4). Logistic regression analysis revealed that birth weight centile (P < 2.3) is the strongest predictor for an abnormal outcome on the ASQ (Odd's ratio 3.6 compared to a birth weight above the 10th percentile) (Table 5).

Table 5
The joint effect of factors of influence on the ASQ in a logistic regression analysis.

	Odds Ratio	**95% Confidence Interval**
MAIN score > zero (n=66)	1.4	0.7 - 2.6
Birth weight centile		
<p 2.3 (n=48)	3.6	1.5 – 8.8
p2.3 – p5 (n=68)	2.1	0.9 – 4.9
p5 – p10 (n=67)	2.6	1.1 – 6.0
>p10 (n=80)	reference	
Education of mother		
Lower professional school (n=129)	2.1	0.7 – 6.0

Discussion

This study shows that there are no significant differences in developmental or behavioral outcomes at 2-years of age in children born at term with a clinical suspicion of growth restriction between a policy of induction of labor, compared to expectant management. The long-term follow-up of the DIGITAT-trial is unique in its prospective design, studying neurodevelopmental and behavioral outcomes of these children and simultaneously comparing different management strategies.
Others have previously shown that at term growth restriction can have long-term consequences on development, however, this was studied in children born SGA and not suspected of IUGR23-25 before birth.
Important is that children with a lower birth weight centile perform worse on the Ages and Stages questionnaire, especially those below the 2.3rd centile. Children admitted to an intermediate level of care and children with a higher MAIN score, also scored worse on the ASQ. Even though we found no differences, not in direct

neonatal outcome nor in the long term follow-up, between a policy of induction compared to expectant management, more children become severely growth restricted (<p 2.3) after a policy of expectant management. On the other hand, after a policy of induction, more children were admitted to an intermediate level of care.
No factors were found to be associated with the increase of behavioral problems at 2-years of age. Behavioral problems may not yet have become evident at this age26. Previous studies have shown effects of IUGR on behavioral outcome at later age, but all for children older than 2-years of age. A longer follow-up period is possibly needed to investigate behavioral problems in children born at term with growth restriction.
In this study we used postal questionnaires to assess neurodevelopmental and behavioral problems in these children. Unfortunately, a complete history and physical examination was non affordable within our study budget and with a postal enquiry we obtained information on the long-term outcome in growth-restricted infants and were able to compare the outcome at two years of age for the two management strategies.
The response rate in the induction group was significantly higher when compared to the expectant management group. An explanation could be that the induced women had better memory of the trial due to the intervention and the fact that their child had to be admitted to hospital more frequently. Another possible response bias could occur because parents of children who are performing poorly and have more problems would be less likely to participate in follow-up studies27. Mothers who responded to the questionnaires smoked less, were older and more frequently Caucasian than non-responders. These characteristics are found more often in groups who are more likely to participate in studies28. Furthermore there were no differences between the responders in the induction group compared to the expectant management group in any of the baseline variables, so we currently do not have any indications of bias.
In conclusion, severe growth restriction (< p 2.3) and neonatal admission seem to be the most important predicting factors for neurodevelopmental problems at 2-years of age in children born after suspected IUGR at term. As induced babies are

admitted more frequently, but more babies become severely growth restricted after expectant management the challenge determining the optimal time to deliver remains. The negative effects of being born relatively premature must be weighed against the negative effects of becoming severely growth restricted. Further studies are needed to investigate patient and fetal factors to delineate those pregnancies in which the fetus is actually growth restricted. If we can predict what fetus will reach its own growth potential and what fetus will cease to grow, we might foresee those who may actually benefit from induction. By that means we could attempt to limit unnecessary neonatal admissions due to iatrogenic late prematurity. Also more detailed follow-up measures and studies in later life are needed in this group to study behavior, IQ, development and motor function of children born at term with growth restriction.

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Chapter 10

Comparison of induction of labor and expectant monitoring in intrauterine growth restriction at term through integration of trial outcomes and patient preferences

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Abstract

Objective: Intrauterine growth restriction (IUGR) is associated with an increased risk for neonatal morbidity and mortality. When diagnosed at or near term, a possible treatment for IUGR is induction of labor. In DIGITAT, a large Dutch multicentre randomized controlled trial (RCT), we found no differences in neonatal outcome or mode of delivery between induction of labor and expectant management. The aim of this patient's preference study alongside the RCT was to gain insight into how women value different obstetrical outcome scenarios. These values, in combination with the outcome distribution of the RCT, will indicate the preferred treatment in women with suspected IUGR after 36 weeks of pregnancy.

Methods: In the DIGITAT trial, 626 women with IUGR at term were randomized for induction of labor or expectant management. We used case scenarios ('vignettes'), involving five important factors ('attributes') that were evaluated by 24 trial participants using a discrete choice experiment (DCE) and by visual analogue scale (VAS). We combined these outcome valuations with outcome distributions of the RCT, and calculated a mean outcome for the strategies induction of labor and expectant management, respectively. These mean values were compared between the treatment groups using t-test for the total group and for subgroups, which were defined according to parity and gestational age.

Results: Using the DCE there was no overall treatment preference for the total group or for any of the subgroups ($p=.72$). The VAS, however, did indicate preference towards expectant management for the total group ($p<.001$) as well as for subgroups.

Conclusion: Based on the theoretical superiority of the DCE over the VAS method, the DCE results are leading. Patient's preferences for expectant monitoring and induction of labor in case of IUGR at term are equal. These results reflect the outcomes of the DIGITAT trial.

Introduction

Evaluation of medical interventions in clinical problems is often difficult because various outcomes are involved. In obstetrics, not only survival, but also the long-term health of mother and child, as well as complications with short-term consequences and the mode of delivery all should be considered in the decision which intervention is the best. An example of an obstetric problem where various outcomes need to be considered is intrauterine growth restriction (IUGR) at term. In pregnancies complicated by IUGR at term there is an increased risk for neonatal morbidity and perinatal mortality, and there is concern about the long term health of the child [1-5]. In case of IUGR at term, there are two treatment options: The pregnancy can be monitored expectantly, or labor can be induced. Induction of labor might prevent neonatal morbidity and perinatal mortality and it may improve long-term outcomes, but it also interferes with the process of natural birth at a possible increased risk of instrumental delivery.

In the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT; ISRCTN10363217), a large nationwide multicentre randomized controlled trial (RCT), induction of labor was compared to expectant monitoring in women with an IUGR-fetus beyond the 36th week of pregnancy. The study showed that in both strategies neonatal morbidity, the number of instrumental deliveries, and maternal outcomes were not different. There were also no differences in overall maternal health-related quality of life (HR-QoL) [6-8]. It was concluded that both strategies appear equivalent in terms of neonatal and maternal health. However, in the accompanying editorial it was stated that, as the association between suboptimal growth and stillbirth is well accepted, it is appropriate to counsel the women because in a suspected growth-restricted pregnancy beyond 36 weeks, induction of labor may prevent the rare but devastating outcome of stillbirth. Whereas this strategy does not increase maternal risk, it might be the preferred option for many women [9].

Alongside DIGITAT we performed a patients' preference study, in which patients

gave their valuations of different health outcome scenarios that were measured in DIGITAT. By combining true DIGITAT outcome data with the patients' valuations of those outcomes, the result is an overall valuation of the outcomes in terms of preference from patients' point of view. Regarding the equivalency of the DIGITAT outcomes, patients' preference can be put forward as the most important indicator for the evaluation of all outcomes taken together in the ultimate choice of treatment [10].

In this paper we present the expected patients' preference of treatment in case of IUGR at term. The treatment options are induction of labor or expectant monitoring. We combined the DIGITAT outcomes with patients' valuations of those outcomes. We evaluated preferences for the total group, as well as for subgroups based on gestational age and obstetric history.

Methods

General approach

The clinical data originated from DIGITAT (Disproportionate Intrauterine Growth Intervention Trial At Term ISRCTN10363217 [6], a multicentre randomized controlled trial (RCT) performed in the Netherlands between November 2004 and November 2008. The 650 included patients with a singleton pregnancy beyond 36+0 weeks gestation with suspected IUGR were randomly allocated to either induction of labor within 48 hours or to expectant management. Main outcome measure was a composite of adverse neonatal outcome, defined as neonatal death before hospital discharge, a 5-minute Apgar score < 7, an umbilical artery pH <7·05 or admission to the neonatal intensive care unit. More details are provided in the original paper [8].
To arrive at the comparison of the patients' preference between induction of labor and expectant management in case of IUGR at term, we made three steps. First, we developed and tested case scenarios among women who had participated in the DIGITAT study and women who were asked but had refused. Second, we combined

the obtained patients' valuations' with the observed clinical outcome data of the DIGITAT study, as well as rates obtained from the literature. From this combined dataset we calculated sum-scores for patients' preferences per treatment allocation (induction or expectant management), and tested for differences between the treatments. Below we discuss these three steps.

Step 1: Development of case scenarios ('vignettes')

In the development of case scenarios, we first aimed to identify the most important factors that were involved in the choice between induction of labor and expectant monitoring. To do so, we conducted interviews about the physical, psychological, and social burden and consequences of IUGR in a previous study [11]. The interviewees were 10 women who participated in DIGITAT or HYPITAT (Hypertension and Preeclampsia Intervention Trial at Term [12] studies, and 10 medical experts (gynecologists, obstetricians, neonatologists, pediatricians). The interviews led to the definition of potential attributes: 'Maternal health ante partum', 'time between diagnosis and delivery', 'process of delivery', 'maternal outcome', and 'neonatal outcome'. Each attribute incorporated several levels. For example, in case of the attribute process of delivery, we considered the attributes spontaneous onset of labor versus induction and primary caesarean section, as well as the mode delivery (vaginal, vacuum or caesarean section), in all possible combinations (Table 1). For each attribute, we defined two to seven levels according to the interviewees' responses, literature review, and expected primary and secondary outcomes from DIGITAT. More information about the vignettes is provided in a separate publication on this study (Bijlenga, Birnie, Bonsel, 2009 [11].

Step 2: Obtaining patient valuations of case scenarios

Patients' valuations of the vignettes were established in group sessions [13]. Participants were 24 patients (other than the pilot participants) who participated to either DIGITAT or to a similar RCT about treatment preference in case of pregnancy-induced hypertension (the HYPITAT trial [12]. All participants valued the vignettes using the widely used weighting method discrete choice experiment (DCE) [13]. The

DCE is believed to be a valid method to calculate utility and preference [14;15]. We also show the results based on the visual analogue scale (VAS) values, which are not considered as a measure of preference, but may give support to the DCE outcomes [16;17]. The mean assigned weights using the methods in our previous study are shown in Table 1. Higher DCE and VAS valuation indicate higher preference. For example, the attribute 'Neonatal outcome' has lower preferences the worse the description of the levels. This indicates less preference of the higher levels of neonatal outcomes as compared to the baseline neonatal level 'No complications'.

The health-related quality of life (HR-QoL) outcomes of the DIGITAT patients were also used in this study [6;7]. As part of the HR-QoL, the participating women filled out the European Quality of life (EQ5D) at inclusion, 6 weeks postpartum, and 6 months postpartum. The EQ5D is a brief validated measure that provides a global health state rating of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [18]. Details of the DIGITAT HR-QoL study are described elsewhere [8]. Using the HR-QoL outcomes we calculated the weights for the attributes Maternal health ante partum and for Maternal outcome (post partum), see also Table 1.

Step 3: Combining patient valuations and outcome data of the DIGITAT trial

In order to combine the patient valuations of the vignettes and the outcome data of the DIGITAT trial, we needed to define which DIGITAT outcomes can be assigned to which level of the attributes. Therefore, we defined 'translation rules' (see Table 1). Most DIGITAT cases could be assigned using the translation rules, see Table 1. Some cases, however, were unclear to which of two adjacent levels they should be assigned. We presented these ambiguous cases to three neonatologists and asked them to which of the two adjacent levels they should be assigned.

Whereas we did not have any data on neonatal mortality from the DIGITAT trial, we used perinatal and neonatal mortality incidence data from the Dutch neonatal registry (PRN 2009) for the calculation of preference for the total group. These data are presented in Table 1 (attribute 5, level 5).

Table 1
Translation rules to assign every clinical case to a level per attribute using observed clinical data from DIGITAT, and its DCE value (significant values are signed by *).

Attribute	Used variable(s)	Level	Translation rules	DCE values patients	DCE values Lay people
A1: Maternal health ante partum	- RCT data: fetal movement, fetal cardiotocography (CTG).	L1	All of the following: EQ Mobility<3; EQ Pain/Discomfort<3; EQ Anxiety/Depression<3; normal fetal movement; good fetal CTG.	Ref	Ref
	- HR-QoL data at inclusion: EQ Mobility, Pain/Discomfort, Anxiety/Depression	L2	At least one of the following: EQ Mobility=3; EQ Pain/Discomfort=3; EQ Anxiety/Depression=3; decreased fetal movement; suboptimal fetal CTG.	0.3	-0.8
A2: Time between diagnosis and delivery	- RCT data: number of days between inclusion date and delivery date.	L1	≤ 3 days	Ref	Ref
		L2	> 3 days	5.3*	-0.6
A3: Process of delivery	- RCT data: induction of labor and mode of delivery.	L1	Vaginal delivery	Ref	Ref
		L2	Induction of labour and vaginal delivery	2.3	-6.2*
		L3	Vacuum or forceps	3.9	-1.4
		L4	Induction of labour and vacuum or forceps	11.3	-1.1
		L5	Primary caesarean	9.3	1.1
		L6	Secondary caesarean	9.3	2.6
		L7	Induction of labour and secondary caesarean	2.5	2.3
A4: Maternal outcome	- RCT data: maternal length of hospital stay, type of hospital stay. - HR-QoL data at 6 months post partum: EQ Mobility, Pain/Discomfort.	L1	All of the following: No stay; stay at the ward; ≤ 5 days stay at Medium care; EQ Mobility<3; EQ Pain/Discomfort<3.	Ref	Ref
		L2	At least one of the following: 6 to 10 days stay at Medium care; < 5 days stay at High or Intensive care with ≤ 10 days total stay; EQ Mobility<3; EQ Pain/Discomfort<3.	-7.2	-4.3*
		L3	At least one of the following: > 10 days stay at Medium care; ≥ 5 days stay at High or Intensive care; EQ Mobility=3; EQ Pain/Discomfort=3.	-12.6*	-16.3*
A5: Neonatal outcome	- RCT data: neonatal length of hospital stay, type of hospital stay, type of complications; diagnosis at discharge.	L1	No hospital stay or stay at maternal ward.	Ref	Ref
		L2	Stay at Medium care ≤ 10 days.	7.6*	-2.3
		L3	At least one of the following: > 10 days stay Medium care; ≤ 5 days at high or intensive care; total hospital stay ≤ 14 days; diagnosis at discharge is not chronic disease.	1.0	-6.8*
		L4	At least one of the following: > 5 days at High or Intensive care; diagnosis at discharge is chronic disease.	-9.3*	-20.8*
		L5	Perinatal or neonatal death.	-13.8*	-33.1*

We combined the clinical dataset and the patient's valuations, using the translation rules. For example, if treatment X resulted in 11% and treatment Y in 9% secondary caesarean sections, and the preference value for caesarean section is -0.2, then the summed score for caesarean section in treatment X is -0.2*0.11= -0.022 and for treatment Y is -0.2*0.09= -0.018. In this example treatment Y is the preferred option since its sum-score is higher. Using paired t-test (in case of normal distributions) we made straightforward comparisons of the summed score for preference for induction of labor versus expectant monitoring. We compared both the preference scores for the total group as well as for subgroups based on gestational age at inclusion (≤ 36+6, 37 to 38+6, and ≥ 39 weeks) and parity (nulliparous, multiparous). Analyses were conducted with SPSS 16.0 for Windows (SPSS Inc). A p-value ≤0.05 (two sided) was considered to indicate statistical significance.

Results

For this study we used data of all 650 randomized DIGITAT women, of which 321 women had been randomized for induction of labor and 329 for expectant management.

All maternal and procedural data could be directly translated to the attributes using the translation rules (Table 1). However, of the neonatal cases, 42 could not be straightforwardly translated to the either of the levels. A panel of three neonatologists assigned 11 of these neonatal cases to Attribute 5 (neonatal outcome), level 3 (A5L3) and 31 cases to A5L4 (Table 1). After the translation of all clinical outcomes into the appropriate attributes and levels, the outcome distributions for the total group and for the subgroups emerged (Table 2).

Table 2
Observed outcome distribution in percentages according to treatment (20), for each attribute-level separately, for all patients and for the subgroups of patients based on parity and gestational age at inclusion. For an explanation of the Attributes and levels, see table 1.

			Subgroups: parity				**Subgroups: gestational age at inclusion**					
Attribute (A) and Level (L)	Total group N=650		Nullipara n=383		Multipara n=266		G1 n=165		G2 n=383		G3 n=101	
	IL	EM	IL	EM	IL	EM	IL	EM	IL	EM	n=383	EM
A1L1	88.8	85.7	87.9	88.1	89.9	82.0	90.1	79.8	89.3	88.2	84.1	86.2
A1L2	11.2	14.3	12.1	11.9	10.1	18.0	9.9	20.2	10.7	11.8	15.9	13.8
A2L1	87.2	11.9	86.6	12.4	88.5	11.0	84.0	11.9	87.2	9.6	93.2	19.3
A2L2	12.8	88.1	13.4	87.6	11.5	89.0	16.0	88.1	12.8	90.4	6.8	80.7
A3L1	3.4	40.2	3.3	37.8	3.6	44.1	2.5	27.2	2.0	44.9	11.4	43.1
A3L2	74.1	37.8	61.3	31.3	90.6	48.0	75.0	42.2	76.0	38.0	63.6	31.0
A3L3	0.3	3.7	0.6	5.5	0	0.8	0	3.6	0.5	2.7	0	6.9
A3L4	8.1	4.6	14.4	7.0	0	0.8	6.3	4.8	7.1	4.3	15.9	5.2
A3L5	0.6	3.4	1.1	3.0	0	3.9	0	6.0	1.0	2.1	0	3.4
A3L6	0	2.1	0	3.0	0	0.8	0	1.2	0	1.6	0	5.2
A3L7	13.4	8.2	19.3	12.4	5.8	1.6	16.3	14.5	13.3	6.4	9.1	5.2
A4L1	97.4	99.1	95.4	99.0	100	99.2	98.7	97.6	97.3	9.4	95.3	100
A4L2	1.0	0.6	1.7	0.5	0	0.8	1.3	1.2	0.5	0.6	2.3	0
A4L3	1.6	0.3	2.9	0.5	0	0	0	1.2	2.1	0	2.3	0
A5L1	48.8	59.4	42.5	53.8	56.8	68.0	27.5	44.6	55.1	64.9	59.1	63.2
A5L2	32.2	21.5	35.9	24.9	27.3	16.4	40.0	21.7	29.6	22.2	29.5	19.3
A5L3	15.0	13.5	17.1	15.7	12.2	10.2	26.3	21.7	11.2	10.3	11.4	12.3
A5L4	4.1	5.5	4.4	5.6	3.6	5.5	6.3	12.0	4.1	2.7	0	5.3
A5L5	0.001*	0.005*	0	0	0	0	0	0	0	0	0	0

Note: IL= Induction of labor; EM= Expectant monitoring; G1= Gestational age ≤ 36+6 weeks at inclusion; G2= 37 to 38+6 weeks; G3= ≥ 39 weeks.
* Data from the Dutch neonatal registry (PRN 2009)

From the calculation of the valuation per attribute, we calculated the valuation distributions for the total group and for the subgroups using the patients' DCE and VAS valuations. All distributions were considered normal. The results of the t-test comparisons between the treatment options for the total group and for the subgroups are shown in Table 3. The table shows overall preference for expectant management in the total group as well as in the subgroups. The DCE preferences were equal between treatment options for both the total group and the subgroups. The VAS outcomes showed a treatment preference for expectant monitoring in the total group (p<.001) as well as for several subgroups (see Table 3).

Table 3
Comparison of the overall preference score according to treatment (20), for all patients and for the subgroup of patients, using the significant patient's and lay people's DCE values. Higher scores indicate stronger preference.

	DCE patient's valuations *			DCE lay people's valuations		
(Sub)groups	IL Mean (SD)	EM Mean (SD)	p	IL Mean (SD)	EM Mean (SD)	p
Total group (N=650)	-0.57 (2.39)	-0.51 (2.11)	.717			
Total group with PRN data	-0.59 (2.39)	-0.58 (2.11)	.945			
Subgroup Nullipara (n=383)	-0.79 (2.82)	-0.54 (2.17)	.326			
Subgroup Multipara (n=266)	-0.28 (1.60)	-0.46 (2.03)	.434			
Subgroup G1 (n=165)	-0.63 (2.35)	-1.05 (2.96)	.336			
Subgroup G2 (n=383)	-0.61 (2.50)	-0.26 (1.53)	.102			
Subgroup G3 (n=101)	-0.29 (1.92)	-0.54 (2.19)	.570			
Subgroup Nullipapa*G1 (n=95)	-0.89 (2.76)	-1.05 (2.97)	.780			
Subgroup Nullipara*G2 (n=204)	-0.86 (2.99)	-0.27 (1.58)	.082			
Subgroup Nullipara*G3 (n=65)	-0.34 (2.34)	-0.52 (2.16)	.884			
Subgroup Multipara*G1 (n=59)	-0.29 (1.64)	-1.03 (2.98)	.231			
Subgroup Multipara *G2 (n=164)	-0.32 (1.72)	-0.24 (1.48)	.733			
Subgroup Multipara *G3 (n=30)	0.00 (0.00)	-0.58 (2.32)	.359			

* The highly improbable significant weight for A5L2 has been ignored.
Note: G1= Gestational age ≤ 36+6 weeks at inclusion; G2= 37 to 38+6 weeks; G3= ≥ 39 weeks.

Discussion

We have taken all RCT data outcomes together and evaluated these in terms of patients' preference for induction of labor or expectant management in case of IUGR at term. We compared the summed valuations of the DIGITAT outcomes [8].

Our results show that, taken the outcomes of the total group, the DCE method did not indicate one preferred treatment over the other. The VAS indicated expectant management as an overall treatment preference. Also for most of the subgroups, which have been established according to the patient's parity and gestational age, the VAS indicated preference towards expectant management. These findings are supplemental to, and a reflection of, the outcomes of the clinical trial [8]. These results do not indicate either induction of labor or expectant management to be superior in terms of patient's preferences.

The DCE as a measure of preference is considered theoretically superior to the VAS. However, both the VAS and the DCE have their limitations. First of all, our main choice of method was the DCE method, which has proven to be a valid preference elicitation method in health care [19]. However, as our previous research has indicated, the outcome may depend on the choice of method [11]. We have backed up the DCE outcomes by VAS outcomes, which gave different results. According to the VAS outcomes, expectant management is superior in terms of patient's preferences. However, the DCE outcomes are here the leading outcomes, which do not reflect superiority of any treatment. Second, in this paper we solely discuss patient's preferences, while previous study shows that doctor's and the general public's preferences may differ[13]. We have limited our focus to patients, whereas in practice, patients are the key decision-makers in this particular setting. Finally, our study has focused on preference elicitation on the group level. Individual preferences may be different from the outcomes on the group level. We have observed in the DIGITAT trial that most patients did not want to participate as randomized patients indicated they wanted to wait instead of being randomized with a 50% chance of

induction of labor [8]. This prior preference for expectant management is reflected in the VAS results, but not in the DCE results. While this does not mean that the DCE is a less valid valuation method, it does seem to reflect revealed preferences less accurate than the VAS.

In short, the equivalence of the patient's preference scores for treatments in case of IUGR after 36 weeks of gestation reflects the equivalence of the clinical DIGITAT outcomes. Both treatments are safe and result in equal maternal and neonatal outcomes and preferences.

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Chapter 11

Suspected versus non-suspected small-for-gestational age fetuses at term: perinatal outcomes

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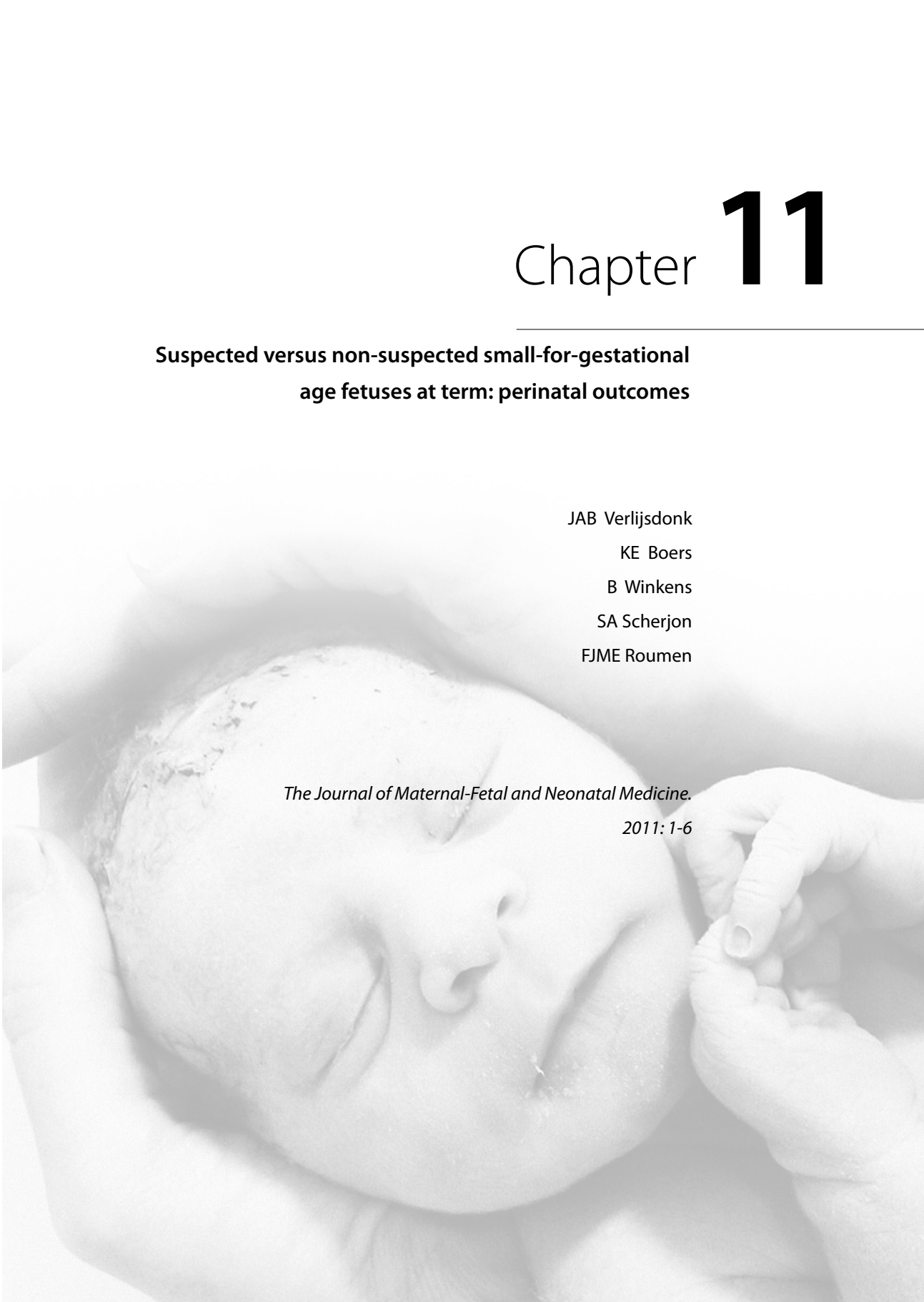

Abstract

Objective: To compare perinatal outcomes of suspected versus non-suspected small-for-gestational age fetuses (SGA) at term.
Methods: Retrospective cohort study among all term singleton neonates with a birth weight <10th percentile born in the Parkstad region between 01-01-2006 and 03-31-2008. The subjects were assigned to a prenatally Suspected or Non-Suspected SGA group. Primary outcome was adverse neonatal outcome at birth, defined as a composite of intrauterine fetal death, Apgar <7 at 5 minutes, or pH umbilical artery <7.05. Secondary outcome included neonatal medium care unit (NMCU) admission ≥7 days.

Results: 430 subjects were included in the study; 36.7% was suspected of SGA. In the Suspected SGA group mean gestational age at birth and birth weight were significantly lower, whereas maternal morbidity was significantly higher. The incidence of labor induction and elective cesarean section were also significantly higher in the Suspected SGA group. Total perinatal mortality was 2.1%. Identification of SGA and subsequent management led to a significant decrease of adverse neonatal outcome at birth, but did not lead to a significant decrease in NMCU admission >7 days.

Conclusions: Suspicion of SGA was associated with a more active management of labor and delivery, resulting in a better neonatal outcome at birth.

Introduction

Perinatal mortality in the Netherlands has gradually decreased from 10.9 per thousand births in 1999, to 10.0 in 2004, and to 9.7 in 2007. This decreasing trend, however, is slower than in other European countries, resulting in a public and political debate on the organisation of obstetric care in the Netherlands[1]. A major contributing factor to perinatal mortality is the small-for-gestational age (SGA) fetus [2-4]. Between 2000 and 2009, perinatal mortality rate in the Netherlands in SGA pregnancies was 1.79% [5]. SGA is also associated with an increased neonatal morbidity [6-7]. Effects of SGA persist well beyond the neonatal period. Children with a history of SGA lag behind in somatic growth, neurodevelopmental performance, cognition and school achievements [8]. SGA is associated with an increased late life prevalence of cardiovascular disease [9].

Improving the prognosis of the SGA fetus by providing effective clinical management is a great obstetrical challenge. In case SGA is suspected based on fundal height measurement, the diagnosis can be confirmed by ultrasound. Identifying SGA in low risk pregnancies is difficult [10-13]. The detection rate after abdominal palpation as a screening test by first line midwives subsequently confirmed by ultrasound, was 15% in a Dutch trial among 6318 singleton pregnancies [14]. In a clinical setting in Sweden, 63% of all SGA fetuses were identified prenatally [15].
There are no effective therapies to improve the growth pattern of the growth restricted fetus [16]. Monitoring the SGA fetus by ultrasound, Doppler and cardiotocography may enable the treating physician to modulate the intensity of the controls and to precisely define the timing of delivery, when necessary [17-18]. When optimal maternal and fetal monitoring can be provided, expectant management and labor induction have equivalent fetal and maternal outcomes [19].

The aim of this retrospective cohort study was to analyze the effect of suspicion and subsequent management of SGA at term in common daily practice on perinatal outcomes, in a well-defined region in the Netherlands.

Methods

The study population consisted of all term (370 - 420 weeks' gestation) singleton SGA neonates born between January 1, 2006 and March 31, 2008, in the Parkstad Heerlen region. Most babies were delivered in the Atrium Medical Centre Parkstad under supervision of an obstetrician, others were delivered at home or in the hospital under supervision of a midwife of the Obstetrical Cooperate Association Heerlen.

Selection of the patients was based on the information available in their medical records. Eligible patients were assigned to a group with prenatally Suspected SGA or a group with prenatally Non-Suspected SGA. SGA was defined as a birth weight <10th percentile, based on weight curves provided by the Netherlands Perinatal Registration. SGA was considered suspected when this was described unambiguously in the mothers' pregnancy chart. The clinical surveillance protocol used in case of prenatally suspected SGA comprised of fetal ultrasounds with fetal-placental Doppler velocimetry weekly, and cardiotocography twice weekly or more frequently depending on the severity of the growth restriction.

Baseline characteristics of the mother and the neonate, characteristics of pregnancy, labor and delivery, and perinatal outcomes were abstracted from the medical files. Maternal baseline characteristics included age at delivery, height, BMI, smoking, use of drugs, alcohol or fetotoxic medication (e.g. SSRI's, antiepileptic drugs), parity, and hypertensive disorders during pregnancy. Neonatal baseline characteristics included gestational age at birth, birth weight and sex. Variables concerning pregnancy, labor and delivery included the moment of referral to the obstetrician, initiation of labor, analgesia, mode of delivery, and delivery complications.
The primary outcome was the composite "adverse neonatal outcome at birth" defined as intrauterine death, Apgar <7 at 5 minutes, or pH umbilical artery <7.05. Secondary outcomes included resuscitation, congenital anomalies, neonatal complications (ranging from hypoglycemia to infections to encephalopathy) and neo-

natal medium care unit (NMCU) admission ≥7 days. A NMCU is equipped for neonates born after at least 32 weeks' gestation who may need artificial ventilation for a maximum of 24 hours.

Categorical variables are presented by number and percentage. Continuous variables are presented by mean and standard deviation. The Chi-square or Fisher's exact test was performed for categorical variables, and the independent-samples t-test for continuous variables. Logistic regression was used to determine the effect of suspicion of IUGR on adverse neonatal outcome at birth as well as NMCU admission ≥7 days after correction for the clinically and statistically most important maternal and neonatal variables, where the maximum number of variables is restricted by the total number of events. Variables with more than 5.0% missing data were not included in the logistic regression analysis, where the robustness of the results was tested by comparing them with those obtained after adding these variables to the model. The effect of suspicion of SGA and other variables on adverse neonatal outcome at birth and NMCU admission ≥7 days were presented by the odds ratio with corresponding 95% confidence interval. Linearity assumption was checked by adding and testing a centered quadratic term, leaving this term in the model when significant.
Results were considered statistically significant when the p-value was < 0.05. Statistical analysis was performed using the SPSS program (version 17.0).

Results

Between January 1, 2006 and March 31, 2008, 4247 women were delivered of a term singleton neonate in the Parkstad region [5]. From these neonates, 430 (10.1%) had a birth weight <10th percentile and were enrolled in the study. 158 (36.7%) of these SGA neonates were suspected prenatally and assigned to the Suspected SGA group. The remaining 272 (63.3%) neonates were assigned to the Non-Suspected SGA group.

In home deliveries (n=40), not all variables used in this study were consequently documented. For the total cohort, this resulted in missing data in the variables maternal length (6.5%), maternal BMI (19.8%), placenta weight (8.1%), umbilical artery pH (9.1%) and umbilical vein pH (10.9%). Of all other variables less than 0.1% of the data was missing.

Maternal baseline characteristics are shown in Table 1. Compared to the Non-Suspected SGA group, mothers in the Suspected SGA group were significantly taller and had a significantly lower BMI. Significantly more women in this group were smokers, used drugs, had an SGA in a previous pregnancy, and had hypertensive disorders during pregnancy.

Table 1
Maternal baseline characteristics

	Suspected SGA group (n=158)	**Non-Suspected SGA group(n=272)**	**p-value**
Age at delivery (years) (mean, SD)	28.4 (5.8)	29.4 (5.4)	0.069
Height (m) (mean, SD)	1.66 (0.07)	1.65 (0.07)	0.021
BMI (kg/m2) (mean, SD)	27.0 (5.2)	28.8 (4.6)	0.001
Smoking (n)	100 (63.3%)	107 (39.5%)	<0.001
Drugs (n)	23 (14.6%)	11 (4.1%)	<0.001
Alcohol (n)	9 (5.7%)	10 (3.7%)	0.330
Fetotoxic medication (n)	9 (5.7%)	13 (4.8%)	0.684
Multigravida (n)	85 (53.8%)	163 (59.9%)	0.215
IUFD* previous pregnancy (≥24 weeks) (n)	3 (3.5%)	4 (2.5%)	0.694
SGA previous pregnancy (n)	44 (51.8%)	56 (34.4%)	0.008
Hypertensive disorders (n)	23 (14.6%)	21 (7.7%)	0.024
Proteinuria (n)	17 (10.8%)	18 (6.6%)	0.130

* Intrauterine Fetal Death

Table 2 shows the neonatal baseline characteristics. Mean gestational age and birth weight were significantly lower for neonates in the Suspected SGA group

compared to the Non-Suspected SGA group. Significantly more neonates had a birth weight < p2.3 in the Suspected SGA group.

Table 2
Neonatal Baseline Characteristics

	Suspected SGA group (n=158)	**Non-Suspected SGA group(n=272)**	**p-value**
Gestational age at birth (days) (mean, SD)	275.1 (9.1)	280.2 (7.8)	<0.001
Birth weight (g) (mean, SD)	2518.1 (331.7)	2770.7 (270.7)	<0.001
Birth weight			<0.001
<p2.3 (n)	68 (43.0%)	66 (24.3%)	
>p2.3 - <p5 (n)	39 (24.7%)	73 (26.8%)	
>p5 - <p10 (n)	51 (32.3%)	133 (48.9%)	
Male sex (n)	74 (46.8%)	142 (52.2%)	0.283

As shown in Table III, 94.9% of women in the Suspected SGA group had prenatal care by an obstetrician, in contrast to 53.7% of women in the Non-Suspected SGA group. In the Suspected SGA group, induction of labor and elective cesarean section were more frequently performed, whereas instrumental delivery and secondary cesareans were more common in the Non-Suspected SGA group. The incidence of meconium stained amniotic fluid was significantly lower in the Suspected SGA group compared to the Non-Suspected SGA group, as were the incidence of episiotomy or a 2nd, 3rd or 4th degree rupture, the mean amount of blood loss, the incidence of blood transfusions, and the mean placental weight.

Table 3
Characteristics of pregnancy, labor and delivery

	Suspected SGA group (n=158)	Non-Suspected SGA group(n=272)	p-value
Moment of referral to obstetrician			<0.001
Primary pregnancy attendance by obstetrician (n)	64 (40.5%)	84 (30.9%)	
Referred to obstetrician during pregnancy (n)	86 (54.4%)	62 (22.8%)	
Referred to obstetrician during delivery (n)	8 (5.1%)	86 (31.6%)	
Referred to obstetrician post partum (n)	0 (0.0%)	40 (14.7%)	
Initiation of labor			<0.001
Spontaneous (n)	101 (63.9%)	225 (82.7%)	
Induction (n)	37 (23.4%)	33 (12.1%)	
Elective cesarean section (n)	20 (12.7%)	14 (5.1%)	
PROM* (n)	11 (8.3%)	30 (11.8%)	0.298
Augmentation* (n)	37 (27.0%)	76 (29.3%)	0.624
Analgesia			0.302
No analgesia (n)	73 (46.2%)	139 (51.1%)	
Oral / systemic analgesia (n)	45 (28.5%)	72 (26.5%)	
Epidural analgesia (n)	9 (5.7%)	23 (8.5%)	
Spinal / General analgesia(n)	31 (19.6%)	38 (14.0%)	
Mode of delivery			0.034
Spontaneous (n)	113 (71.5%)	201 (73.9%)	
Instrumental (n)	13 (8.2%)	28 (10.3%)	
Elective cesarean section (n)	20 (12.7%)	14 (5.1%)	
Secondary cesarean section (n)	12 (7.6%)	29 (10.7%)	
Meconium stained amniotic fluid (n)**	36 (22.8%)	92 (33.8%)	0.016
Mean length of 2nd stage of labor (min) (mean, sd)***	17.9 (18.8)	22.4 (22.5)	0.056
Episiotomy or 2nd/3rd/4th degree rupture (n)***	70 (55.6%)	154 (67.2%)	0.029
Mean blood loss (ml) (mean, sd)	362.5 (262.6)	440.9 (371.0)	0.011
Blood transfusion (n)	1 (0.6%)	14 (5.1%)	0.014
Mean weight placenta (g) (mean, sd)	475.4 (93.8)	522.5 (97.7)	<0.001

*** All except elective cesarean section
*** All except intrauterine deaths
*** All except cesarean section

Table 4 presents the perinatal results. In the Suspected SGA group the incidence of adverse neonatal outcome at birth was lower compared to the Non-Suspected SGA group (3.8% vs. 9.0%, p= 0.056). Nine children died, resulting in a total perinatal mortality of 2.1%. In the Suspected SGA group, 2 children died during labor. In one case a dying fetal heart rate tracing was recorded in the outpatient department, and the fetus died before an emergency cesarean section could be performed. In the other case, the pregnant woman was seen early in labor with few fetal movements, but was sent back home as the fetal heart rate tracing was mistakenly judged reassuring. Several hours later she presented with an intrauterine fetal death.

In the Non-Suspected SGA group, six women had an intrauterine fetal death; three were caused by placental insufficiency, and one by a partial placental abruption, whereas in two women only positive neonatal and placental cultures were diag-

Table 4
Perinatal results

	Suspected SGA group (n=158)	**Non-Suspected SGA group(n=272)**	**p-value**
Composite adverse neonatal outcome at birth	6 (3.8%)	21 (9.0%)	0.056
Perinatal mortality total (n)	2 (1.3%)	7 (2.6%)	0.496
During pregnancy (n)	0	6 (2.2%)	
During labor (n)	2 (1.3%)	0	
After delivery (n)	0	1 (0.4%)	
Live birth (n)	156 (98.7%)	266 (97.8%)	0.716
Apgar 1′ <7(n)	11 (7.1%)	32 (12.0%)	0.103
Apgar 5′ <7 (n)	3 (1.9%)	9 (3.4%)	0.548
pH umbilical artery <7.05 mol/L (n)	1 (0.6%)	9 (3.9%)	0.054
pH umbilical vein <7.05 mol/L (n)	0 (0.0%)	4 (1.8%)	0.151
Resuscitation (n)	16 (10.3%)	34 (12.8%)	0.438
Consultation pediatrician (n)	152 (96.2%)	237 (87.1%)	0.002
Admission NMCU (n)	90 (57.7%)	98 (36.8%)	<0.001
Congenital anomalies (n)	11 (7.0%)	15 (5.5%)	0.550
Admission NMCU >7 days (n)*	55 (35.3%)	37 (13.9%)	<0.001
Neonatal complications total (n)	87 (55.8%)	112 (42.3%)	0.007

* All except the neonate that died after delivery

nosed without clinical signs of an intrauterine infection. Furthermore, in the Non-Suspected SGA group one neonate died 3 days after emergency cesarean section for fetal distress. In this case it was decided to stop treatment because of irreversible cerebral damage.
In the Suspected SGA group significantly more neonates needed consultation of a pediatrician, were admitted to the NMCU, stayed there >7 days, and had common complications like hypothermia, hypoglycemia, hyperbilirubinemia, respiratory distress, and infections.

Table 5 shows that the crude odds ratio adverse neonatal outcome at birth when comparing Suspected with Non-Suspected SGA at term, was 0.40 ([95% CI 0.16-1.02]; p=0.056). After correction for birth weight and hypertensive disorders, it was found that identification and subsequent labor and delivery management led to a significant decrease of adverse neonatal outcome at birth (OR 0.28 [95% 0.10-0.79]; p= 0.016).

Table 5
Multivariable logistic regression on adverse neonatal outcome at birth

	Odds Ratio (95% CI)	p-value	Corrected Odds Ratio (95% CI)	Corrected p-value
Suspected SGA	0.40 (0.16-1.02)	0.056	0.28 (0.10-0.79)	0.016
Birth weight	1.00 (0.99-1.00)	0.538	0.99 (0.99-1.00)	0.171
Maternal hypertensive disorders	2.45 (0.93-6.45)	0.069	2.56 (0.94-6.98)	0.067

* All except the neonate that died after delivery

Table 6 shows that the crude odds ratio for NMCU admission ≥7 days when comparing suspected with non-suspected SGA at term, was 3.37 ([95% CI 2.09-5.44]; p= <0.001). After correction for gestational age at birth, birth weight, maternal smoking, drug abuse and hypertensive disorders, it was found that suspicion and subsequent labor and delivery management did not lead to a significant decrease in NMCU admission ≥7 days (OR 1.02 [95% CI 0.53-1.97]; p= 0.950). Similar results were obtained when the variables with >5.0% missing data were added to the model.

Lower birth weight and maternal hypertensive disorders were independently associated with NMCU admission ≥7 days. For babies with a birth weight <p2.3, only birth weight and not maternal hypertensive disorders was independently associated with NMCU admission ≥7 days (data not shown).

Table 6
Multivariable logistic regression on NMCU admission >7 days

	Odds Ratio (95% CI)	p-value	Corrected Odds Ratio (95% CI)	Corrected p-value
Suspected SGA	3.37 (2.09-5.44)	<0.001	1.02 (0.53-1.97)	0.950
Gestational age at birth	0.91 (0.88-0.94)	<0.001	1.03 (0.99-1.08)	0.138
Birth weight	0.99 (0.99-1.00)	<0.001	0.99 (0.99-1.00)	<0.001
Maternal smoking	1.33 (0.84-2.12)	0.226	0.82 (0.43-1.55)	0.533
Maternal drug abuse	3.70 (1.80-7.59)	<0.001	2.39 (0.89-6.37)	0.083
Maternal hypertensive disorders	3.71 (1.93-7.12)	<0.001	3.22 (1.30-8.01)	0.012

Between January 1, 2006 and March 31, 2008, 4247 women were delivered of a term singleton neonate in the Parkstad region [5] From these neonates, 430 (10.1%) had a birth weight <10th percentile and were enrolled in the study. 158 (36.7%) of these SGA neonates were suspected prenatally and assigned to the Suspected SGA group. The remaining 272 (63.3%) neonates were assigned to the Non-Suspected SGA group.
In home deliveries (n=40), not all variables used in this study were consequently documented. For the total cohort, this resulted in missing data in the variables maternal length (6.5%), maternal BMI (19.8%), placenta weight (8.1%), umbilical artery pH (9.1%) and umbilical vein pH (10.9%). Of all other variables less than 0.1% of the data was missing.

Maternal baseline characteristics are shown in Table 1. Compared to the Non-Suspected SGA group, mothers in the Suspected SGA group were significantly taller and had a significantly lower BMI. Significantly more women in this group were smokers, used drugs, had an SGA in a previous pregnancy, and had hypertensive disorders during pregnancy.

Table 2 shows the neonatal baseline characteristics. Mean gestational age and birth weight were significantly lower for neonates in the Suspected SGA group compared to the Non-Suspected SGA group. Significantly more neonates had a birth weight < p2.3 in the Suspected SGA group.

As shown in Table 3, 94.9% of women in the Suspected SGA group had prenatal care by an obstetrician, in contrast to 53.7% of women in the Non-Suspected SGA group. In the Suspected SGA group, induction of labor and elective cesarean section were more frequently performed, whereas instrumental delivery and secondary cesareans were more common in the Non-Suspected SGA group. The incidence of meconium stained amniotic fluid was significantly lower in the Suspected SGA group compared to the Non-Suspected SGA group, as were the incidence of episiotomy or a 2nd, 3rd or 4th degree rupture, the mean amount of blood loss, the incidence of blood transfusions, and the mean placental weight.

Table 4 presents the perinatal results. In the Suspected SGA group the incidence of adverse neonatal outcome at birth was lower compared to the Non-Suspected SGA group (3.8% vs. 9.0%, p= 0.056). Nine children died, resulting in a total perinatal mortality of 2.1%. In the Suspected SGA group, 2 children died during labor. In one case a dying fetal heart rate tracing was recorded in the outpatient department, and the fetus died before an emergency cesarean section could be performed. In the other case, the pregnant woman was seen early in labor with few fetal movements, but was sent back home as the fetal heart rate tracing was mistakenly judged reassuring. Several hours later she presented with an intrauterine fetal death. In the Non-Suspected SGA group, six women had an intrauterine fetal death; three were caused by placental insufficiency, and one by a partial placental abruption, whereas in two women only positive neonatal and placental cultures were diagnosed without clinical signs of an intrauterine infection. Furthermore, in the Non-Suspected SGA group one neonate died 3 days after emergency cesarean section for fetal distress. In this case it was decided to stop treatment because of irreversible cerebral damage.

In the Suspected SGA group significantly more neonates needed consultation of a pediatrician, were admitted to the NMCU, stayed there >7 days, and had common complications like hypothermia, hypoglycemia, hyperbilirubinemia, respiratory distress, and infections.
Table 5 shows that the crude odds ratio adverse neonatal outcome at birth when comparing Suspected with Non-Suspected SGA at term, was 0.40 ([95% CI 0.16-1.02]; p=0.056). After correction for birth weight and hypertensive disorders, it was found that identification and subsequent labor and delivery management led to a significant decrease of adverse neonatal outcome at birth (OR 0.28 [95% 0.10-0.79]; p= 0.016).

Table 6 shows that the crude odds ratio for NMCU admission ≥7 days when comparing suspected with non-suspected SGA at term, was 3.37 ([95% CI 2.09-5.44]; p= <0.001). After correction for gestational age at birth, birth weight, maternal smoking, drug abuse and hypertensive disorders, it was found that suspicion and subsequent labor and delivery management did not lead to a significant decrease in NMCU admission ≥7 days (OR 1.02 [95% CI 0.53-1.97]; p= 0.950). Similar results were obtained when the variables with >5.0% missing data were added to the model. Lower birth weight and maternal hypertensive disorders were independently associated with NMCU admission ≥7 days. For babies with a birth weight <p2.3, only birth weight and not maternal hypertensive disorders was independently associated with NMCU admission ≥7 days (data not shown).

Discussion

The incidence of SGA in the Parkstad region (10.1%) was similar to the incidence of SGA in the Netherlands (10.0%) based on the Netherlands Perinatal Registration curves [5].
SGA was suspected in only 36.7% of cases, which is remarkably lower than the 63.0% found in a Swedish study [15]. A possible explanation for this low detection

rate is, that the Swedish study was a clinical setting, whereas our study included pregnancy attendance by primary care midwifes at home as well. Estimating fetal weight is commonly performed only by abdominal fundal height measurement without a standardized protocol [16]. Ultrasound was only used when SGA was suspected and not as a routine procedure. The sensitivity of detecting SGA by measuring the fundal height is higher when the pregnant mother has a lower BMI, as was demonstrated in this study. The relatively lower birth weight in the Suspected SGA group, which can be derived from the higher incidence of a birth weight ≤2.3 percentile in this group, confirms that suspicion of SGA is also easier when the fetus is smaller. SGA was suspected more frequently in mothers who smoked, used drugs, had an SGA in a previous pregnancy, or had hypertensive disorders. This was presumably because obstetric care workers are more alert for SGA in these pregnancies [19].

The high percentage of non-suspected cases of SGA in this and other studies [10-15] is of great concern. It remains a diagnostic challenge to identify those fetuses at risk of true SGA. Optimization of diagnostic tools is urgently needed, as both abdominal fundal height measurement and routine ultrasonography are insufficient to estimate fetal weight below the 10th percentile correctly [20-21]. In a German study, serial ultrasound measurements of fetal weight resulted in detection of only 30% of the SGA fetus [11]. Customized growth centile charts are rarely applied in the Netherlands, but might identify the fetus at risk [13-22].

Suspicion of SGA led to more active management. Gestational age at birth was significantly lower in the Suspected SGA group, which can be partly explained by the higher incidence of labor inductions and elective cesarean sections in this group. This is in accordance with other studies [11-23-24].

Logistic regression analysis showed, that suspicion of SGA followed by a more active management of labor and delivery resulted in better neonatal outcomes at birth. This is in contrast with other studies, which reported that these interventions are associated with higher rates of obstetrical complications and neonatal morbidity [18-25-28]. As suggested by a previous study active management is likely to be

advantageous for a genuine intrauterine growth restricted (IUGR) subpopulation that do not reach, because of inadequate placental function, their genetic growth potential. However, such a management might be detrimental for the constitutionally SGA fetuses who follow their own growth trajectory during pregnancy [29]. Due to lack of data in this specific cohort, a reliable differentiation in to one of these groups (SGA or IUGR) is not feasible.
Perinatal mortality in this study was 2.1%, which is comparable with other studies [2-5-30]. During the same period the incidence of perinatal mortality in term singleton pregnancies not complicated by SGA in the Parkstad region was significantly lower; 5 in 3817 babies (0.13%) (RR 15.67; [95% CI 5.28-46.6]; p= <0.001) [5]. This indisputably marks the importance of SGA as a risk factor for perinatal mortality. Whenever SGA at term is suspected, the pregnant women should be closely and continuously monitored as of the early stage of labor. In the recently published multicentre DIGITAT study in the Netherlands, in which 650 women with suspected IUGR at term were randomized to induction or expectant monitoring, no stillbirths or perinatal deaths occurred [19]. A possible explanation for this favorable outcome is that in the randomized controlled DIGITAT trial the pregnant women with suspected SGA may have been monitored more intensively than in regular daily practice. Suspicion of SGA and subsequent active management or intensive monitoring might have prevented the death of the fetus in at least the three cases of placental insufficiency in the Non-Suspected SGA group. However, even in the Suspected SGA group management of labor and delivery was not active enough to prevent the two cases of intrauterine fetal death. This pleads for more intensive monitoring and active management in pregnancies complicated by SGA at term.

In the Suspected SGA group, significantly more neonates were seen by a pediatrician, as this is routine policy in our O&G Department when SGA is suspected. Moreover, in this group significantly more neonates were admitted to the NMCU. The rate of NMCU admission ≥7 days was significantly higher in the Suspected SGA group. This can be explained by the significantly higher prevalence in the suspected SGA group of neonatal complications associated with low birth weight, ranging

from predominantly hypoglycemia to infections and incidentally encephalopathy. Identification and subsequent management of pregnancy, labor and delivery had no significant effect on the incidence of NMCU admission ≥7 days, whereas birth weight and maternal hypertensive disorders were independently associated with NMCU admission ≥7 days.

The main strength of this retrospective study is that it provides a better insight in common daily practice in a well-defined region in the south of the Netherlands without the bias of a study setting which is intrinsically to randomized controlled trials.
This study has some limitations. A limited amount of data was missing, as is common in retrospective studies. Midwives performing home deliveries are instructed to admit neonates with a birth weight <10th percentile to the pediatrician at the Atrium Medical Centre. It is possible, that a few healthy neonates with a good start were not referred to the obstetrician, leading to underreporting. In the Suspected SGA group, 39 women participated in the DIGITAT or HYPITAT trial [19-31]. From these patients, 15 underwent induction of labor as a result of randomization. So the number of inductions in this group might be overrepresented.

In conclusion, most cases of SGA were not suspected during pregnancy in this retrospective study. SGA was predominantly suspected in women who were carrying a very small fetus, had a lower BMI, who smoked, used drugs, had a previous SGA, or had hypertensive disorders. Suspicion of SGA led to a more active management of labor and delivery. This resulted in better neonatal outcomes at birth, but was not active enough to prevent two cases of fetal death in the Suspected SGA group. Identification of SGA and a more active management also had no significant influence on the incidence of NMCU admission ≥7 days, which was associated with the lower birth weight of the neonates and the higher prevalence of maternal hypertensive disorders in this group.

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Chapter 12

General discussion and future perspectives.

General discussion and future perspectives.

Intrauterine growth restriction is a major cause of perinatal morbidity and mortality[1-5]; not only immediately after birth but also on the long term it can affect a child`s health.[6-8]
Until recently, evidence from a RCT considering timing of delivery in at term IUGR was lacking.[9] This thesis evaluates two different management strategies in at term growth restriction. We compared timing of delivery by planned, elective induction of labour with expectant management including fetal surveillance and monitoring of the mother in singleton pregnancies with cephalic presentation complicated by suspected intrauterine growth restriction beyond 36 weeks gestational age. The RCT aimed to show that both strategies were equivalent regarding adverse perinatal outcomes. Under the provision that both strategies are equally safe we would be able to perform secondary analysis such as comparing intervention rates, costs, maternal quality of life and long-term (neuro)development of the children.

Principle findings

- *In a retrospective Dutch cohort of small for gestational age (SGA) babies born with a birth weight below the 10th percentile between 2000 and 2005, we found that induction of labour after 36 weeks gestation was associated with a higher risk of emergency caesarean section (CS), without improvement in neonatal outcome.* Pregnant women with isolated SGA were more than 2 times likely and women with both SGA and hypertensive disorders were almost 3 times more likely to have emergency CS after induction compared to women with a spontaneous onset of labour. We concluded that prospective studies are needed to determine the best strategy in suspected IUGR at term.

- *The DIGITAT trial, central in this thesis, concluded that both induction of labour as well as an expectant management policy with monitoring of mother and child are*

safe strategies in at term IUGR. We found no perinatal deaths in either of the two groups, nor any difference in umbilical artery pH below 7.05, 5-minute Apgar below 7 or NICU admissions.

- Maternal morbidity was comparable between the two strategies. *Induction of labour did not lead to higher rates of vaginal operative deliveries or an increase of emergency caesarean sections.*

- *The trial is underpowered for finding differences in stillbirth, therefore it is reasonable to induce labour to pre-empt this most devastating outcome in IUGR pregnancies.*

- We found that *significantly more babies were admitted to intermediate type of neonatal care (high care and medium care) after a policy of induction.* The induced group babies were delivered on average 10 days earlier and subsequently weighing 130 grams less compared to expectant management babies.

- *More children get severely growth restricted after a policy of expectant management (<P 2.3).*

- To define if the excess of neonatal admissions were protocol driven due to the fact that these children were smaller and younger or if these children were in fact sicker, neonatal morbidity was examined in detail by assessing the MAIN-score. *The MAIN-score was comparable for both induction group babies as well as for expectant management group babies.* In at term IUGR neonatal morbidity is relatively mild. However, for both strategies more children had a positive MAIN-score when born before 38 weeks gestational age, as compared to children born beyond 38 weeks gestation. *For as long as neonatal and maternal condition is reassuring, it is reasonable to prevent neonatal admissions by delaying delivery beyond 38 weeks gestational age in at term IUGR.*

- We explored generalisability of the results by assessing external validity of the trial. We compared outcomes of women who refused to participate to outcomes of participants of the DIGITAT trial. Although these non-participants were in general healthier (i.e. they had lower BMI, smoked less and were higher educated), they tended to have less favourable outcomes. Only among non-participants 3 babies died. *We showed that participating in a RCT on IUGR did not increase the risk of bad outcome. We even proposed that participation in a RCT may be good for pregnant women.*

- We examined maternal health-related quality of life after induction of labour or expectant monitoring in pregnancy alongside the trial at several points in time. No clinically relevant differences between the two strategies at 6 weeks or 6 months post partum on any summary measures were found. Women in both groups showed lower scores on the mental component (MCS) of short form (SF-36) at all time measurements, showing lower mental health compared to an average Dutch population. *In short, induction of labour in at term IUGR does not affect the long-term maternal quality of life.*

- As both strategies were comparable in terms of physical and mental health outcomes, we performed a cost-minimisation analysis in which only the direct medical costs of both strategies were compared. Induction generated more direct medical costs, because of longer stay in the labour room and more neonatal high care and medium care admissions. Expectant management had an excess of ante partum costs due to maternal admissions for maternal and fetal monitoring. Altogether, *we showed comparable costs for induction and expectant management.*

- *Patient's preferences for expectant management and induction of labour in case of IUGR at term are equal.*

- We assessed (neuro)developmental outcome and behavioural problems of the

children at two years of age by postal questionnaires:1) the Ages and Stages Questionnaire (ASQ), and 2) the Child Behavior Checklist (CBCL). *We found no significant differences in developmental or behavioural outcomes at 2-years of age. Severe growth restriction (P<2.3) and neonatal admission were found to be the most important predictive factors for (neuro)developmental problems at 2 years of age* in children born after suspected IUGR at term.

- In a retrospective study of neonates born between January 1, 2006 and March 31, 2008, we found that most cases of SGA were not identified as such. SGA was predominantly detected in women who were carrying a very small fetus, had a lower BMI, who smoked, used drugs, had a previous IUGR, or had hypertensive disorders. Suspicion of *SGA led to a more active management of labour and delivery. This resulted in better neonatal outcomes at birth compared to IUGR not suspected during pregnancy.* Not all cases of fetal death in the Suspected IUGR group can be prevented.

Strengths, limitations and implication

The main strength of the DIGITAT study is the randomised comparison of two delivery and management strategies in suspected IUGR at term. We advise induction of labour in at term IUGR beyond 38 weeks gestational age to pre-empt perinatal mortality, providing maternal and fetal monitoring.

No other appropriate randomised control trials in this particular area have been performed. This prospective approach was feasible through collaboration of more than 50 hospitals embedded within the structure of the Dutch obstetric consortium.[10] Academic hospitals, general teaching as well as non-teaching hospitals participated to the DIGITAT trial, throughout the country. This has resulted in a study population , which reflects a general population of pregnant women suspected of at term IUGR, and makes the results generally applicable. Like the smaller randomised pilot trial we found comparable neonatal and maternal outcomes.[11] This equipoise of induction and expectant management is in contrast to findings of the

HYPITAT trial where maternal outcomes as well as the operative delivery rates were in favour of induction of labour.[12] For at term IUGR both strategies are safe.
The strength of this prospective study lies in the fact that it demonstrates safe management in suspected IUGR at term, rather than discussing treatment strategies with the knowledge of SGA in hindsight. In March 2008, before the results of the DIGITAT trial were known, Dutch gynaecologists and residents were asked for their opinion about at term IUGR through questionnaires. They assumed that induction of labour would increase the rate of caesarean sections and only a minority assumed that it would lower the rate of CS (Chapter 1). This was in agreement with our findings from a retrospective study (Chapter 2), where we found higher rates of operative deliveries after induction of labour. In contrast, we did not observe higher operative delivery rates after induction of labour in the trial, which is in accordance with recent prospective intervention trials.[12-14] There are several alternatives to explain this contradiction between our retrospective and prospective findings. In our observational study only children born SGA are included and therefore selection took place by looking back at children with the highest risk. Additionally, we do not know if SGA was identified or not in these children. In our prospective study children were suspected of IUGR. Some of these children were born with a birth weight above P10, may be also due to the fact that they were induced, averting further growth restriction. This also might be the reason for a lower risk for operative delivery. Since the operative deliveries were comparable between the two strategies it seems reasonable to induce labour to pre-empt stillbirth. For as long as neonatal and maternal condition is reassuring, delaying delivery beyond 38 weeks gestational age may prevent neonatal admissions, because the MAIN-scores as well as neonatal admissions were higher at week 36 and 37 (Chapter 4).

Additional strength of the study is that we tested external validity and generalisability of data by examining non-participants in the same prospective way.[15-17] While none of the children of participating women died, perinatal deaths did occur among non-participants. Since all deaths were after a relative long period of expectant monitoring, these findings might imply that waiting too long for spontane-

ous delivery in IUGR imposes risk of perinatal morbidity and mortality, imaginably also due to the lack of protocol driven management. Our data are in accordance with many other studies suggesting that participation in a randomised trial or protocol driven management improves outcomes regardless of the actual treatment given.[18-20] Probably both obstetricians and patients are more alert to their medical status when they participate in a study.
Even when study results seem applicable to other populations it does not automatically mean that the policies are also applicable in these populations.[21] The results of the DIGITAT study should be extrapolated with caution to settings where close monitoring cannot be offered, e.g. in less-developed countries or in women who are unlikely to follow instructions or redraw from fetal monitoring.
A limitation of the study is that women whose fetus was already presumed to be at high risk (e.g. because of fetal brain-sparing) were excluded from randomisation and were induced.[22] Likewise other women, whose pregnancy was not presumed to be at risk (e.g. still growing along its own growth curve), were not included because of fear for unnecessary and possible harmful inductions. This inclusion bias might have affected external validity of the trial.[16] By prospectively following non-participants we addressed inclusion bias to a certain extent. However, to examine outcomes of eligible pregnant women who beforehand were excluded by their doctors is impossible.

The fact that induction of labour in IUGR does not affect the long-term maternal quality of life is a very relevant finding. Also in women with gestational hypertension or pre-eclampsia QoL was unaffected by induction.[23] May be induction of labour relieves a feeling of insecurity for these women with complicated pregnancies. In both groups of randomised women with at term IUGR after 6 months of age mental health stayed below the mean Dutch and U.S. mental component score outcomes. Probably worries or anxiety about the child's health persist in both groups even after 6 months of age. This is in contrast to women with hypertension complicating pregnancy who showed equal to population average MCS scores 6 weeks and 6 months after childbirth.[23]

The DIGITAT trial is the first RCT that includes an economic analysis of labour management and outcomes in at term IUGR. Unfortunately we have no data on health care utilisation after hospital discharge for the randomised women. Therefore we do not know if medical costs, sick leave from work (indirect non-medical costs), mode of travelling to hospital and the use of informal care given by partner and/ or family (direct non-medical costs) were different between the two strategies.
Since for both strategies the rate of neonatal admissions is lower beyond 38 weeks gestation, we speculate that delaying delivery up to 38 weeks would be more cost-effective, as compared to induction before 38 weeks gestational age.

The DIGITAT RCT is the only study that looked at long-term outcomes of children suspected of IUGR after labour induction or expectant management prospectively. We have shown that severe growth restriction (<P 2.3) and neonatal admissions are the most important predicting factors for (neuro)developmental problems at 2-years of age in children born after suspected IUGR at term.
Unfortunately, a complete history and physical examination at 2 years of age was not feasible with our budget. Therefore we sent out questionnaires to most of the women in the study. Response rates were 54% in the induction group and 46% in the expectant group. This might have lead to non-response bias: we cannot exclude that children with worse outcomes were not in this analysis, possibly leading to different outcomes showing superiority of one of the two strategies.
The DIGITAT trial was not powered to detect perinatal mortality as this would require thousands of women, which was not feasible.
Lack of power is probably the main reason why we did not detect perinatal deaths in the trial. There are two other possible explanations for the discrepancy between prospective (no perinatal deaths in the randomised DIGITAT study) and retrospective findings (associations between IUGR and perinatal mortality). Firstly, the DIGITAT women were identified as having IUGR. As we found in our study described in chapter 13 suspicion of IUGR is associated with active management of labour and delivery, resulting in a better neonatal outcome at birth compared to cases where

diagnosis was missed. The fact that we found that identification of IUGR favours neonatal outcomes is in contrast to other studies that showed higher intervention rates without improving neonatal outcomes after identification of IUGR.24;25 Secondly, women as well as doctors are probably more alert because they participate in a trial, presumably inflicting active management as soon as conditions deteriorate. Positive effects of this vigilance may well be shown in the non-participants study (Chapter 6), where 3 perinatal deaths did occur among non-participants, most likely due to the lack of protocol-driven management, even though they were suspected to be too small.

The challenge of screening and treating IUGR is to distinguish before childbirth fetuses with (genuine) growth restriction and those that are constitutionally small. We included women who were suspected of IUGR and defined IUGR by fetal abdominal circumference (FAC) < P10, estimated fetal weight (EFW) < P10, flattening of the growth curve, or combinations of these inclusion criteria, as measured with ultrasound. We included them irrespective of Doppler recordings and irrespective of individualised customised growth. Recent observational studies show that in term growth restriction decreased Medial Cerebral artery Pulsatility Index (MCA-PI), indicative of fetal brain-sparing, could be a proxy for adverse neonatal outcome at term, independently of UA-PI.22 This screening tool for determining the optimal timing of delivery in at term IUGR has not been investigated in randomised trials yet.
Since MCA-PI was not routinely used by the start of the DIGITAT trial in 2004, we do not know which fetuses might have suffered from brain-sparing at term. Also customised growth curves are not routinely applied in the Netherlands as a screening tool.

Future Perspectives

Whereas important questions about at term IUGR have been answered, several questions exist, and are substrate for further analysis and set-up of future studies.

The crux in IUGR is to detect children with genuine growth restriction. Individualising fetal growth might help to identify fetuses suffering from genuine growth restriction.[26-28] Although not defined as a primary outcome in our study, we have collected the determinants of customised birth weight curves prospectively, i.e. maternal height and weight, smoking, racial background, EFW, sex and gestational age. We plan to calculate *customised growth curves* to examine if these curves will better predict which children have genuine growth restriction and who might benefit from induction.

Since *MCA-Doppler* recordings have been done prospectively in 57 patients we plan to analyse them and associate the outcomes with neonatal outcomes and operative deliveries.

Catch up growth, crossing of neonatal birth weight percentiles, is one of the possible important characteristic of genuine IUGR which however can only be determined after birth. Catch-up growth is also associated with early origins of insulin resistance and obesity.[29] We asked trial participants to fill out length and weight of the children at several moments in time during the two year follow-up and we will look at catch-up growth of these children and compare the two strategies.

In addition evaluation of *Ponderal index and subcutaneous fat distributions* as measured by subscapular and triceps skinfold thickness are within the scope of future secondary analyses of the DIGITAT trial. With the knowledge of true growth restriction after birth, we might be able to determine before birth the risk factors and characteristics of these children. By this means it could provide new insights in the selection of children that might benefit of induction.

Plans to study *influences of IUGR on blood pressure, obesity and insulin resistance, as well as school performance and (neuro)development on the even longer term* (e.g. 10 years of age) have been made.

A different approach to identify the fetus at highest risk for adverse outcome is to search for additional diagnostic markers to improve the detection of children with an EFW below the 3rd percentile. By developing a *diagnostic risk score,* among women suspected of having intrauterine growth restriction (IUGR) at 36 to 41 weeks, that can differentiate between an estimated fetal weight < vs. > 3% for gestational age, we would be able to detect a vulnerable group of children. Validation of the score could be performed in the non-participant group of women and in different retrospective cohorts. These studies are underway.

The DIGITAT study population was diverse and it is conceivable that not all women have the same a-priori risks of adverse outcome. Treatment selection markers are biomarkers that can prospectively identify individuals who are likely to benefit from a specific treatment, separating them from individuals for whom the more limited health gains do not outweigh the safety and side effects of treatment.30 We will examine possible biomarkers from the DIGITAT data to evaluate their prognostic value as *treatment selection markers* in at term IUGR. By this means we try to advance to determine the best strategy by tailoring the treatments for at term IUGR.

Conclusion

IIn conclusion, induction of labour and expectant management, while strictly monitoring mother and child both are safe strategies in at term growth restriction. Concerning obstetrical and neonatal outcomes - not only immediately after birth, but also on the long-term, health costs, maternal quality of life and maternal preferences, both strategies are comparable. To pre-empt the devastating outcome of stillbirth it is reasonable to induce labour after 38 weeks of gestation.

Hypothetically we could prevent 1 neonatal admission due to complications of relative prematurity, by delaying induction in 10 pregnancies suspected of IUGR beyond 38 weeks. Further delaying delivery to later gestational ages will increase the proportion of severely growth restricted children (<P 2.3) which is not desirable. To determine genuine growth restriction and to detect the fetuses at highest risk for adverse outcome remains a great challenge. Customised growth, development of diagnostic risk scores and integration of UA-, and MCA-Doppler recordings are entries for future studies in at term IUGR. By development of treatment selection markers we can evaluate if tailor-made treatment for the individual women whose pregnancy is complicated by growth restriction at term is possible; to induce labour or to await spontaneous delivery with expectant management.

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Chapter 13

Summary

This thesis describes the results of the DIGITAT trial (Disproportionate Intrauterine Growth Intervention Trial At Term) and concentrates on strategies in intrauterine growth restriction (IUGR) at term.

Chapter 1

Chapter 1 forms the introduction of this thesis and gives a set-up to the DIGITAT trial. Around 9% to 11% of children is born with a birth weight below the 10th percentile and defined as small-for-gestational age (SGA). A significant part of these children are born in the term period. Pregnancies complicated by intrauterine growth restriction (IUGR) and children born small-for-gestational-age are known to have higher risk of perinatal mortality and neonatal morbidity, not only immediately after birth but also on the longer term. The terms intrauterine growth restriction (IUGR) and small-for-gestational-age (SGA) have been used interchangeably, creating confusion on the topic. In this way studies looking at associations between smallness and adverse neonatal outcomes have been blurred. In the introduction of this thesis definitions of SGA and IUGR are discussed. The methods to improve screening and identification of IUGR are discussed, as well as an insight in the latest opinions about the importance of Doppler-recordings of middle cerebral artery (MCA). To deal with at term pregnancies complicated by suspicion of IUGR there are two management strategies to approach the fetus at risk for morbidity and mortality. Would the fetus fare better by further growing and maturing in a possible undernourished environment, and thus postponing delivery with an expectant management? On the other hand induction of labour might pre-empt possible morbidity and stillbirth, may be at the cost of an increase in operative deliveries, and complications of relative (iatrogenic) prematurity. Results from prospective randomised trials as well as consensus among Dutch gynaecologists and residents about management and timing of delivery in at term IUGR were lacking. To deal with these questions about the controversial management of IUGR at term the DIGITAT trial (Disproportionate Intrauterine Growth Intervention Trial At Term) was designed. Embedded in the structure of the Dutch Obstetrical Consortium more than 50 hospitals, academic and non-academic, participated to this randomised controlled trial to enrol 650

women whose pregnancy was complicated by suspected IUGR at term. The aim of the study was to compare the effect of induction of labour with an expectant monitoring policy for suspected intrauterine growth restriction at term in singleton pregnancies in cephalic presentation beyond 36 weeks gestation on neonatal and obstetrical outcomes.

Chapter 2

This chapter presents the results of a retrospective cohort of SGA children in the Netherlands. Data of the National Dutch Perinatal Registry (PRN) were used of all nulliparae between 2000 and 2005 with a singleton in cephalic presentation beyond 36+0 weeks, with a birth weight below the 10th percentile. We analysed two groups of pregnancies: (I) with isolated SGA and (II) with both SGA and hypertensive disorders. Onset of labour was related to route of delivery and neonatal outcome. Induction was associated with a higher risk of emergency caesarean section (CS), without improvement in neonatal outcome. For women with isolated SGA the relative risk of emergency CS after induction was 2.3 (95% Confidence Interval [CI] 2.1 to 2.5) and for women with both SGA and hypertensive disorders the relative risk was 2.7 (95% CI 2.3 to 3.1). In concord with other retrospective studies it was concluded from this retrospective cohort that induction in pregnancies complicated by SGA at term was associated with a higher risk of instrumental deliveries without improvement of neonatal outcome.

Chapter 3

The full study protocol of the DIGITAT trial is described in this chapter. All women with a singleton pregnancy, with a child in cephalic presentation, with suspicion of IUGR (Fetal Abdominal Circumference < 10th centile, Estimated Fetal Weight < 10th percentile as defined by local protocols, or decreased relative growth though still > 10th centile) and a gestational age between 36+0 weeks and 41+0 weeks were eligible. Women with a history of caesarean section, serious congenital defects, ruptured membranes, renal diseases, diabetes mellitus, or positive HIV se-

rology were excluded. After written consent, pregnant women suspected of IUGR were randomised by means of a web-based application. Stratification was applied for previous vaginal birth (nullipara versus multipara) and for centre. Patients that withheld consent for randomisation were asked permission for data collection on pregnancy outcome and date were collected in the same prospective way. Before randomisation baseline demographics, past obstetric and medical history were collected for all women and cervical length was measured.
The study was staffed by obstetricians, research nurses, and midwives associated with the Dutch Obstetric Consortium. They counselled and recruited participants, monitored compliance with allocated treatment protocols, and collected outcome data.

Participants were either allocated to an induction of labour group, where induction had to take place within 48 hours of randomisation or to an expectant monitoring group. In the expectant group women had to be monitored until the onset of spontaneous labour with daily fetal movement counts and twice weekly fetal heart rate tracings, ultrasound examination, maternal blood pressure measurement, assessment of proteinuria, laboratory tests of liver and kidney function, and full blood count. Women were monitored as either an outpatient or an inpatient, according to local protocol. In the expectant monitoring group, induction of labour or planned caesarean section was performed for obstetrical indications—such as suboptimal fetal heart rate tracings, prolonged rupture of membranes, or postmaturity between T+7 and T+14 days—at the obstetrician's discretion. Women that were registered as non-participants were treated according to the opinion of their attending doctor with either an induction of labour or an expectant management policy.

The primary outcome was a composite measure of adverse neonatal outcome. This was defined as death before hospital discharge, five minute Apgar score of less than 7, umbilical artery pH of less than 7·05, or admission to neonatal intensive care. Secondary outcomes were delivery by caesarean section, instrumental vagi-

nal delivery, length of stay in the neonatal intensive care or neonatal ward, maternal length of stay in the hospital, and maternal morbidity. The latter was defined as post-partum haemorrhage of more than 1000 mL, development of gestational hypertension or pre-eclampsia (according to International Society for the Study of Hypertension in Pregnancy criteria), eclampsia, pulmonary oedema, thromboembolism, or any other serious adverse event.

Other secondary outcomes were a maternal health-related quality of life study and follow up of children's behavioural-, and (neuro)development by administering postal enquiries: the Child Behaviour Checklist-CBCL and Ages and Stages Questionnaire- ASQ after 2 years. Under assumption of comparable adverse outcomes a cost-minimisation analysis, in which only the costs of both strategies would be compared, was performed.

The trial was designed as an equivalence trial in which the null hypothesis was that the difference in the risk of the composite outcome between the two treatment groups was greater than 5.5% (absolute percentage). Assuming that the rate in the control group was 6% (on the basis of data from the National Dutch Perinatal Registry), this meant that we would exclude the null hypothesis and conclude that the two treatments were equivalent if the boundaries of the confidence interval of the observed risk difference were between -5.5% and 5.5%. With a 0.05 risk of type I error (α) and 80% (1-β) power, we calculated that we would require 650 participants (325 per group).

Data were analysed according to the intention to treat principle. Equivalence of the primary outcome measure was tested by checking if the 95% CI of the risk difference lay within the equivalence margins. Treatment effects were presented as differences in means or percentages with 95% confidence intervals (CI).

Chapter 4

The results of the DIGITAT trial are described in chapter 3. In this multicentre ran-

domised equivalence trial (the Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT)) eight academic and 44 non-academic hospitals in the Netherlands participated to included eligible women between November 2004 and November 2008. A total of 1116 women with a singleton pregnancy in cephalic presentation, with a pregnancy suspected of IUGR beyond 36 weeks gestation were identified. Of these women, 466 declined randomisation, of whom 452 gave authorisation for use of their medical data.

321 women were randomly assigned to induction and 329 to expectant monitoring. Compared with the induction group, women in the expectant monitoring group were more likely to have a Bishop score of less than or equal to 6 and gestational hypertension, but otherwise the two randomised arms were comparable. Women who declined randomisation were older, had a higher education level, were less likely to smoke, had a lower body mass index (BMI), and were less likely to have a fetal abdominal circumference below the 10th centile. Most women who were randomised met either the fetal abdominal circumference below 10th centile inclusion criterion or the estimated fetal weight below the 10th centile criterion. Only 13 women in the induction group and 10 women in the expectant monitoring group were included because of flattening of the growth curve in isolation.

Induction was performed in 306 (95.6%) of the women in the induction group, resulting in a median time from randomisation to onset of labour of 0.9 days (IQR 0.7 to 1.7) in the induction group and 10.4 days (IQR 5.6 to 16.0) in the expectant monitoring group. In the expectant monitoring group labour was induced in 166 (50.6%) women.

Caesarean sections were performed on 45 (14.0%) mothers in the induction group and 45 (13.7%) in the expectant monitoring group (difference 0.3%, 95% CI -5.0% to 5.6%).

One (0.3%) woman allocated to induction of labour died at home 10 days after delivery. She had delivered a healthy child vaginally at 38+4 weeks of gestation after spontaneous onset of labour. No cause for her death was found at postmortem and it was classified as a serious unrelated adverse event. No women in the expectant monitoring group died during the study. All other maternal outcomes were comparable between the two groups.

There were no stillbirths or perinatal deaths. A total of 17 (5.3%) neonates in the induction arm and 20 (6.1%) neonates in the expectant monitoring arm had the primary composite adverse neonatal outcome (difference 0.8%, 95% CI - 4.3% to 2.8%). No differences between groups in any of the components of the composite adverse neonatal outcome were found. Median birth weight was lower in the induction group than in the expectant monitoring group (2420 g v 2550 g; difference 130 g, 95% CI 188 g to 71 g; P<0.001). Despite this difference, more fetuses in the expectant monitoring arm had a birth weight below the third percentile (100 (31%) v 40 (13%); difference 18.1%, 95% CI 24.3% to 12.0%; P<0.001).
More neonates in the induction group were admitted to a ward providing an intermediate level of neonatal care (155 (48.4%) v 118 (36.3%); difference 12.1%, 95% CI 4.6% to 19.7%; P<0.05).

In conclusion, we found equivalent fetal and maternal outcomes for induction and expectant monitoring in women with suspected intrauterine growth restriction at term, indicating that both approaches are acceptable. However, it is rational to choose induction to prevent possible neonatal morbidity and stillbirth on the grounds that we showed no increase in operative and instrumental delivery rates. By inducing labour in cases of intrauterine growth restriction, infants that will not grow any further can be released from their undernourished environment.

Chapter 5
In this chapter we describe details of a sub-analysis, by reporting neonatal morbidity between the two strategies based on a validated morbidity assessment index for newborns (MAIN). This score was developed to provide a numeric index of early neonatal outcomes of prenatal care and adverse prenatal exposures in babies delivered beyond 28 weeks of gestation. This sub-analysis was done mainly because we had found a significant difference in neonatal admissions to an intermediate type of care (48% v. 36%; difference 12%, 95% CI: 5% to 20%, P<0.05) in the DIGITAT trial. Complications of late prematurity might have explained this difference, since children in the induction group were born on average ten days earlier than in the

expectant group (266 days v 277 days; difference -9.9 days, 95% CI: -11 to -9). However, the difference may simply reflect policies for admission to intermediate levels of care related to prematurity rather than clinically relevant morbidity. In addition, more children were severely growth restricted in the expectant group, defined as a birth weight below the third percentile (13% v 31%; difference -18%, 95% CI -24% to -12%) and therefore had a possible higher risk of neonatal morbidity.

The MAIN score was assessed in 308 induction group babies and in 315 expectant management group babies. The categories of the MAIN scores (no/minimal, mild, moderate and severe morbidity) did not differ between the induction and expectant group. Morbidity in at term IUGR was relatively mild, and comparable for both induction and expectant management. When we looked at components of the MAIN score, more children suffered from hyperbilirubinemia >220 mmol/L or the need for phototherapy after induction of labour (n=32 (10.4%) for induction v n=18 (5.7%) for expectant management; difference 4.7%, 95% CI 0.4% to 8.9%, $p<0.05$).

For the outcomes neonatal admissions, a positive MAIN score and composite adverse outcome, we compared induction to an expectant management in women randomised before 38 weeks, from 38 till 40 weeks and after 40 weeks. The only difference was a higher percentage of neonatal admissions after induction before 38 weeks gestational age; 125 (61%) admissions v 92 (44%) after expectant management; difference 16%, 95% CI 6.7% to 26%, p=0.001).

We concluded that the apparent excess of neonatal care admission in the induction arm of the DIGITAT trial was probably a benign side effect of late prematurity and neonatal admission policies, rather than a marker of serious neonatal morbidity. If a policy of induction for near term growth restriction is to be followed, deferring induction until 38 weeks if feasible, while strictly monitoring mother and child, may prevent complications of late prematurity. Late effects of these policies need further study.

Chapter 6

Chapter 6 describes the results of the non-randomised women. All pregnant women who had a singleton pregnancy beyond 36+0 weeks' gestation with suspected intrauterine growth restriction who declined randomisation in the DIGITAT trial, but who gave authorisation for the use of their medical data were registered as non-participants. Identical data were collected prospectively.

The same primary outcome, a composite measure of adverse neonatal outcome (neonatal death before hospital discharge, a 5-minute Apgar score < 7, an umbilical artery pH <7·05 or admission to the neonatal intensive care unit) was used as well as operative delivery. Comparisons were between participants and non-participants, regardless of the group they were randomised to or treatment received.

In addition to 650 randomised women, 452 women consented for use of their medical data. Non-participants were older, had a lower body mass index (BMI), smoked less frequently and had a higher level of education.

A total of 37 (6%) infants of participants experienced the composite adverse neonatal outcome, compared with 32 (8%) in the non-participants (adjusted difference -2.0%, 95% CI -5.2% to 1.1%). In the non-participants group 3 (0.7%) deaths (2 stillbirths, 1 neonatal death) occurred, whereas no perinatal deaths occurred in the randomised group of women (difference -0.7%, 95% CI -1.4% to 0.1%, p=0.06). Caesarean sections were performed on 90 (14%) participants and on 71 (16%) non-participants (adjusted difference -2.8%, 95% CI -7.5% to 1.8%). In almost all comparisons, we found a tendency towards a more favourable neonatal outcome in women who were randomised. After adjustment for baseline imbalances in maternal age, smoking, BMI, education level and hypertensive disorders the adjusted difference and (95% CI) for perinatal death after participation in the trial was -0.5% (-1.4% to 0.4%, p=0.27).

We found a tendency towards more favourable outcomes in women randomised to the DIGITAT trial than in women who refused to participate, even after adjusting for baseline characteristics. We concluded that participation in a randomised clinical trial on growth restriction did not increase the risk of bad outcome. This information can be used when counselling women for trials.

Chapter 7

In this chapter Maternal health-related quality of life after induction of labour or expectant monitoring in pregnancy complicated by intrauterine growth retardation at term is described.

Both randomised and non-randomised women were asked to participate in the health-related quality of life (HR-QoL) study. Women were asked to fill out written validated questionnaires, covering background characteristics, condition-specific issues and the Short Form (SF-36), European Quality of Life (EuroQoL 6D3L), Hospital Anxiety and Depression scale (HADS), and Symptom Check List (SCL-90) at baseline (before and after randomisation), 6 weeks postpartum and 6 months postpartum. We compared the difference scores of all summary measures between the two management strategies by ANOVA. A repeated measures multivariate mixed model was defined to assess the effect of the management strategies on the physical (PCS) and mental (MCS) components of the SF-36. The analysis was by intention to treat. 361 randomised and 198 non-randomised patients were analysed. There were no clinically relevant differences between the treatments (induction or expectant management) at 6 weeks or 6 months postpartum on any summary measures; e.g., on the SF-36 (PhysicalComponentScore (PCS): P = 0.09; MentalComponentScore (MCS): P = 0.48). The PCS and the MCS were below norm values at inclusion. The PCS improved over time but stayed below norm values at 6 months, while the MCS did not improve. Main conclusion was that in pregnancies complicated by IUGR beyond 36 weeks, induction of labour does not affect the long-term maternal quality of life compared to expectant management

Chapter 8

After showing comparable medical outcomes and QoL, the economic impact of the two strategies is analysed. We used a health care perspective, in which only medical costs are included, with a time horizon from randomisation until hospital discharge. Thereby, by documenting details on utilisation of health care resources, we provided insight in the clinical origins of costs associated with management of these high-risk pregnancies. As both strategies were comparable in terms of health

outcomes, we performed a cost-minimisation analysis in which only the costs of both strategies were compared. We differentiated three phases of the clinical process in which costs arise: ante partum costs (from the moment of randomisation until childbirth), costs related to the delivery, and postpartum costs (from the moment of childbirth until hospital discharge). Resource use during the admission period was documented in the Case Report Form (CRF). The following resource items were collected: maternal and neonatal admissions, method of delivery, outpatient visits, medication, maternal laboratory tests, cardiotocograms (CTGs) and fetal ultrasounds. Maternal admissions were differentiated into three levels of care (intensive, medium, or ward). Neonatal admissions were divided into four levels of care (intensive, high, medium, or ward). Ante partum expectant monitoring generated more costs, mainly due to longer ante partum maternal stays in hospital. For the durante partu and postpartum stage, induction generated more direct medical costs, due to longer stay in the labour room and longer duration of neonatal high care/medium care admissions. From a health care perspective, both strategies generated comparable costs: on average € 7,106 per patient for the induction group (N=321) and € 6,995 for the expectant management group (N=329) with a cost difference of € 111 (95%CI: - € 1,296 to € 1,641). We can conclude that in women with pregnancies complicated by IUGR at term, induction of labour generates identical health care costs as compared to expectant management.

Chapter 9

In a secondary analysis we studied long term outcomes looking at 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. Parents of 2-year old children included in the DIGITAT-trial were asked to answer the Ages and Stages Questionnaire (ASQ) and Child Behaviour Check List (CBCL). The Ages and Stages Questionnaire is a screening questionnaire designed to detect developmental delay in children. The Child Behavior Checklist consists of 100 items concerning behavioural problems, on the basis of which a Total Problem score can be computed. It also informs on 7 narrow band syndrome scales (emo-

tionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behaviour), and two broad-band scales (internalizing and externalizing behaviour). We approached 582 (89.5%) of 650 parents. The response rate was 50%. Of these children, 27% had an abnormal score on the ASQ and 13 % on the CBCL. Results of the ASQ and the CBCL for the two policies were comparable. Low birth weight, positive morbidity assessment index (MAIN score) and admission to intermediate care, increased the risk of an abnormal outcome of the ASQ. This effect was not seen for the CBCL. With this secondary analysis we showed that in women with IUGR at term, both a policy of induction of labour and expectant management do not affect developmental and behavioural outcome when compared to expectant management.

Chapter 10

Whereas medical outcomes, maternal health-related QoL, costs and also long-term (neuro)development at 2 years of age of children born after IUGR are comparable between induction and expectant management women's preferences for one of the two strategies become even more interesting. To gain insight into how women value different obstetrical outcome scenarios, we compared induction of labour and expectant monitoring in intrauterine growth restriction at term through integration of trial outcomes and patient preferences. We used case scenarios ('vignettes'), involving five important factors ('attributes') that were evaluated by 24 trial participants using a discrete choice experiment (DCE) and by visual analogue scale (VAS). We combined these outcome valuations with outcome distributions of the RCT, and calculated a mean outcome for the strategies induction of labour and expectant management, respectively. These mean values were compared between the treatment groups using t-test for the total group and for subgroups, which were defined according to parity and gestational age. Using the DCE there was no overall treatment preference for the total group or for any of the subgroups. The VAS, however, did indicate preference towards expectant management for the total group as well as for subgroups. Based on the theoretical superiority of the DCE over the VAS method, the DCE results were leading. Therefore patient's prefer-

ences for expectant monitoring and induction of labour in case of IUGR at term were equal. These results reflected the outcomes of the DIGITAT trial.

Chapter 11

Chapter 11 presents the results from a retrospective cohort study among all term singleton neonates with a birth weight <10th percentile born in the Parkstad region (Heerlen) between 01-01-2006 and 03-31-2008. The aim of the study was to compare perinatal outcomes of suspected versus non-suspected small-for-gestational age fetuses (SGA) at term. The subjects were assigned to a prenatally Suspected or Non-Suspected SGA group. SGA was considered suspected when this was described unambiguously in the mothers' pregnancy chart. The clinical surveillance protocol used in case of prenatally suspected SGA comprised of fetal ultrasounds with fetal-placental Doppler velocimetry weekly, and cardiotocography twice weekly or more frequently depending on the severity of the growth restriction. Primary outcome was adverse neonatal outcome at birth, defined as a composite of intrauterine fetal death, Apgar <7 at 5 minutes, or pH umbilical artery <7.05. Secondary outcome included neonatal medium care unit (NMCU) admission ≥7 days. A total of 430 subjects were included in the study; 36.7% was suspected of SGA. In the Suspected SGA group mean gestational age at birth and birth weight were significantly lower, whereas maternal morbidity was significantly higher. The incidence of labour induction and elective caesarean section were also significantly higher in the Suspected SGA group. Total perinatal mortality was 2.1%. The crude odds ratio of adverse neonatal outcome at birth when comparing Suspected with Non-Suspected SGA at term, was 0.40 (95% CI 0.16-1.02, p=0.056). After correction for birth weight and hypertensive disorders, it was found that identification and subsequent labour and delivery management led to a significant decrease of adverse neonatal outcome at birth (OR 0.28, 95%CI 0.10-0.79, p= 0.016).
Identification of SGA and subsequent management led to a significant decrease of adverse neonatal outcome at birth, but did not lead to a significant decrease in NMCU admissions longer than 7 days. In conclusion suspicion of SGA was associated with a more active management of labour and delivery, resulting in a better neonatal outcome at birth.

Chapter 12

General discussion - principle findings:

- In a retrospective Dutch cohort of children born small for gestational age (SGA) induction of labour after 36 weeks gestation was associated with a higher risk of emergency caesarean section (CS), without improvement in neonatal outcome.
- The DIGITAT trial, basis of the thesis, concluded based on equivalence of the primary outcome of the trial, a composite adverse outcome of neonatal morbidity, that both induction of labour as well as an expectant management policy are safe strategies in at term IUGR.
- Induction of labour did not lead to higher rates of vaginal operative deliveries or an increase of emergency caesarean sections in the DIGITAT study.
- Even though both policies are safe, it is not unreasonable to induce labour to pre-empt the most devastating outcome in IUGR, stillbirth.
- Significantly more babies were admitted to intermediate type of neonatal care (high care and medium care) after a policy of induction of labour.
- More children get severely growth restricted after a policy of expectant management (<P 2.3).
- The MAIN-score was comparable for both induction group babies as well as for expectant management group babies. More children had a positive MAIN-score when born before 38 weeks gestational age, as compared to children born beyond 38 weeks gestation. Therefore, for as long as neonatal and maternal condition is reassuring, it is feasible to defer delivery beyond 38 weeks gestational age in at term IUGR.
- We showed that participating in a RCT on IUGR did not increase the risk of bad outcome, and this information can be used when counselling women for participation in a RCT.
- Induction of labour in at term IUGR does not affect the long-term maternal quality of life.
- From a health-care perspective, induction and expectant management generate comparable costs.

- Patient's preferences for expectant monitoring and induction of labour in case of IUGR at term are equal, and reflects the equivalence of the primary outcomes on top of medical outcomes, costs and QoL.
- We found no significant differences in developmental or behavioural outcomes at 2-years of age in children born at term with a clinical suspicion of growth restriction under a policy of induction of labour v expectant management. Severe growth restriction (P<2.3) and neonatal admission were found to be the most important predictive factors for (neuro)developmental problems at 2 years of age in children born after suspected IUGR at term.
- Suspicion of IUGR compared to cases where IUGR is not identified as such led to a more active management of labour and delivery, resulting in better neonatal outcomes at birth.

In conclusion, induction of labour and expectant management, while strictly monitoring mother and child both are safe strategies in at term growth restriction. Concerning obstetrical and neonatal outcomes - not only immediately after birth, but also on the long-term, health costs, maternal quality of life and maternal preferences, both strategies are comparable. To pre-empt the devastating outcome of stillbirth it is reasonable to induce labour after 38 weeks of gestation.
Hypothetically we could prevent 1 neonatal admission due to complications of relative prematurity, by delaying induction in 10 pregnancies suspected of IUGR beyond 38 weeks. Further delaying delivery to later gestational ages will increase the proportion of severely growth restricted children (<P2.3) which is not desirable. To determine genuine growth restriction and to detect the fetuses at highest risk for adverse outcome remains a great challenge. Customised growth, development of diagnostic risk scores and integration of UA-, and MCA-Doppler recordings are entries for future studies in at term IUGR. By development of treatment selection markers we can evaluate if tailor-made treatment for the individual women whose pregnancy is complicated by growth restriction at term is possible; to induce labour or to await spontaneous delivery with expectant management.

Chapter 14

Nederlandse samenvatting

In dit proefschrift worden verschillende behandel strategieën van a terme groeivertraging beschreven. De DIGITAT trial (Disproportionate Intrauterine Growth Intervention Trial At Term), een multicentrum gerandomiseerde studie is de basis voor dit proefschrift. In deze gerandomiseerde studie werd inleiding van de baring vergeleken met een expectatief beleid bij vrouwen wiens zwangerschap gecompliceerd werd door een a terme intra-uteriene groeivertraging.

Hoofdstuk 1

Hoofdstuk 1 is de introductie van het proefschrift. Het beschrijft de verschillende facetten van a terme groeivertraging en vormt de onderbouwing van de DIGITAT studie. Ongeveer 9% tot 11 % van de neonaten heeft een te laag geboorte gewicht voor de zwangerschapsduur (<P10). Een aanzienlijk deel van deze pasgeborenen wordt geboren op de a terme leeftijd. Zwangerschappen die gecompliceerd worden door groeivertraging hebben een hoger risico op perinatale sterfte en neonatale morbiditeit. Deze kinderen hebben niet alleen direct na de geboorte een hogere kans op morbiditeit, maar ook op latere leeftijd lopen deze kinderen een hoger risico op neurologische ontwikkelingsachterstand en chronische ziekten, zoals diabetes mellitus. Onderzoek naar groeivertraging wordt bemoeilijkt door het feit dat verschillende definities van groeivertraging frequent door elkaar heen worden gebruikt. In de introductie worden de verschillende definities van groeivertraging en te klein voor de leeftijd, zogenaamd small-for-gestational age (SGA), besproken. Vanwege de mogelijk ernstige gevolgen van IUGR is identificatie van groeivertraagde kinderen dus van groot belang. Verschillende screenings methoden om het onderscheid te maken tussen constitutioneel te klein en pathologisch te klein worden besproken. Tevens worden de laatste opvattingen over het belang van cerebrale bloedstroom distributie bij a terme groeivertraging weergegeven. Wanneer eenmaal de verdenking op IUGR is gerezen zijn er in feite twee strategieën om de intra-uterien groeivertraagde zwangerschappen te benaderen. Moet een expectatief beleid gevolgd worden met maternale en foetale bewaking, zodat de kinderen nog kunnen groeien en rijpen, totdat de baring zich spontaan inzet? Of moet de baring ingeleid worden om morbiditeit en eventuele sterfte te voorkomen, mo-

gelijk ten koste van een hoger aantal kunstverlossingen en sectio caesarea, en gevolgen van (iatrogeen geïnduceerde) relatieve prematuriteit van de kinderen? In Nederland bestonden geen richtlijnen die antwoord gaven op vraagstukken rondom groeivertraging op de a terme leeftijd. In 2008 werd een enquête verstuurd naar gynaecologen en arts-assistenten nog voordat de resultaten van de DIGITAT trial bekend werden. De resultaten hiervan geven de verdeeldheid over het onderwerp weer. Om duidelijkheid te krijgen over wat nu de beste benadering is van a terme groeivertraging, inleiden of afwachten, werd de DIGITAT studie opgezet. Met behulp van de infrastructuur van het Nederlands verloskundige consortium werd deze gerandomiseerde studie uitgevoerd in 8 universitaire en 44 niet-universitaire ziekenhuizen. Zo konden 650 vrouwen met een door groeivertraging gecompliceerde a terme zwangerschap gerandomiseerd worden voor inleiden van de baring, danwel voor een afwachtend beleid. De uitvoering van de studie werd mogelijk gemaakt door subsidie van ZonMw, Nederlands doelmatigheidsonderzoek (nummer 945-04-558).

Hoofdstuk 2

Hier worden de resultaten van een retrospectieve studie van een cohort Nederlandse kinderen met een geboortegewicht onder de 10de percentiel beschreven. We gebruikten data van de stichting Perinatale Registratie Nederland (PRN). Alle nulliparae die bevielen tussen 2000 en 2005 van een eenling in hoofdligging na 36+0 weken, met een geboortegewicht onder de 10de percentiel werden geïncludeerd. Twee groepen vrouwen werden bekeken: (I) vrouwen van wie alleen het kind te klein was, en (II) vrouwen die zowel een te klein kind, als ook een zwangerschapshypertensie of pre-eclampsie hadden. Van deze vrouwen werd de invloed van de start van de baring op de wijze van bevallen en de neonatale uitkomsten bekeken. In groep I (alleen klein kind) bleek inleiding geassocieerd met een meer dan 2 keer hogere kans op een sectio caesarea, zonder verbetering van de neonatale uitkomsten, OR 2.3 (95% betrouwbaarheidsinterval (BI) 2.1 tot 2.5). In groep II (klein kind en hypertensieve aandoening) was het risico op een sectio bijna 3 keer zo groot, OR 2.7 (95% BI2.3 to 3.1). Conform andere retrospectieve studies vonden

wij dat inleiding van de baring bij een laag geboortegewicht op de a terme leeftijd was geassocieerd met een hoger risico op een sectio caesarea en vaginale kunstverlossing zonder dat dit resulteert in een betere neonatale uitkomst.

Hoofdstuk 3

In hoofdstuk 3 wordt het volledige studie protocol van de DIGITAT studie beschreven. Vrouwen met een eenlingzwangerschap, met een kind in hoofdligging, bij wie er verdenking was op groeivertraging (gedefinieerd als een echografisch gemeten buikomtrek < P10, een geschat foetaal gewicht onder de P10, of een relatieve groeivertraging door afbuiging van de groeicurve) konden tussen de 36+0 en 41+0 weken geïncludeerd worden. Vrouwen met een sectio caesarea in de anamnese, langdurig gebroken vliezen, nier ziekten, diabetes mellitus, of met positieve HIV serologie en zwangerschappen met een congenitaal afwijkende foetus kwamen niet in aanmerking. Nadat de vrouwen een toestemmingsverklaring hadden getekend werden zij via een web-based computer programma gerandomiseerd. Er werd gestratificeerd voor een eerdere vaginale bevalling (nullipara versus multipara) en voor het deelnemende centrum. Vrouwen die deelname weigerden werden om toestemming gevraagd voor het vervolgen van hun medische uitkomsten en hun gegevens werden op dezelfde prospectieve manier verzameld. Baseline karakteristieken zoals medische en obstetrische voorgeschiedenis werden voor randomisatie verzameld en de cervixlengte werd gemeten.

De studie werd gecoördineerd door gynaecologen en research medewerkers, die aangesloten waren bij het Nederlands verloskundig consortium. Vrouwen die gerandomiseerd werden voor inleiding moesten binnen 48 uur ingeleid worden. Vrouwen die voor de afwacht groep lootten werden vervolgd door middel van ten minste tweewekelijkse CTG controles, anamnese van foetale beweging, tenminste wekelijks echo-onderzoek, bloedonderzoek, en urinecontrole op eiwit. Deze controles werden poliklinisch of tijdens een ziekenhuisopname verricht, afhankelijk van de ernst van de groeivertraging. In de afwachtgroep werd gewacht totdat de baring spontaan op gang kwam, of totdat een primaire sectio nodig vanwege obstetrische indicatie of totdat een inleiding van de baring geïndiceerd was, zoals

bijvoorbeeld bij langdurig gebroken vliezen, een suboptimaal CTG, of bijvoorbeeld vanwege serotiniteit. Vrouwen die geregistreerd werden als weigeraar werden volgens locaal protocol door hun behandelend arts gevolgd.
De primaire uitkomst was een slechte neonatale uitkomst, samengesteld uit sterfte voor ontslag uit het ziekenhuis, een Apgar score lager dan 7 na 5 minuten, een arteriële navelstreng pH van 7·05 of minder of opname op de neonatale intensive care unit (NICU). Secundaire uitkomsten waren het percentage vaginale kunstverlossingen en sectio caesarea, opnameduur op de NICU, maternale opnameduur en maternale morbiditeit, gedefinieerd als maternale sterfte, fluxus post-partum (meer dan 1000 cc bloedverlies), ontwikkeling van zwangerschapshypertensie, pre-eclampsie of eclampsie, longoedeem, diepe veneuze trombose of andere ernstige complicaties.
Als belangrijke overige secundaire uitkomsten werden de maternale kwaliteit van leven en de (gedrags)neurologische ontwikkeling van kinderen op 2 jarige leeftijd onderzocht. Dit laatste gebeurde met de Child Behaviour Checklist (CBCL) en Ages and Stages Questionnaire (ASQ). Er vanuit gaande dat de medische uitkomsten gelijk zouden zijn, werd tevens een kosten-effectiviteits studie uitgevoerd.
De studie werd opgezet als een equivalentie studie met als nul hypothese dat het verschil in risico op de primaire uitkomst tussen de twee groepen groter zou zijn dan 5.5% (absolute percentage). Dat betekende dat we de nul hypothese zouden verwerpen en de twee strategieën gelijk waren als de grenzen van het betrouwbaarheidsinterval van het gevonden risicoverschil zouden vallen tussen -5.5% and 5.5%. Met een type I error (α) van 0.05 en power van 80% (1-β) power, zouden er 650 vrouwen (2x325) geïncludeerd moeten worden. De resultaten werden geanalyseerd volgens het "intention to treat" principe.

Hoofdstuk 4

Hierin worden de primaire en enkele secundaire uitkomsten van de DIGITAT besproken. Tussen november 2004 en november 2008 werden in totaal 1116 vrou-

wen met een eenling zwangerschap in hoofdligging, met en verdenking op groeivertraging vanaf 36 weken gevraagd om deelname. Van hen wilden 466 vrouwen niet gerandomiseerd worden, en van deze 466 vrouwen gaven er 452 toestemming voor het vervolgen van hun medische uitkomsten.
321 vrouwen werden gerandomiseerd voor inleiding van de baring en 329 voor een afwachtend beleid. Vrouwen die in de afwachtgroep zaten hadden vaker een Bishop score van 6 of minder en hadden vaker zwangerschapshypertensie, maar verder waren ze vergelijkbaar bij randomisatie. Vrouwen die als weigeraar werden geregistreerd waren ouder, hoger opgeleid, hadden een lager BMI, rookten minder, en hadden minder vaak een buikomtrek onder de P10 als inclusiecriterium. Van de gerandomiseerde vrouwen hadden de meesten een foetus met een buikomtrek onder de P10, een geschat foetaal gewicht onder de P10, een afbuigende groei, of een combinatie van deze criteria. Slechts 13 vrouwen in de inleidgroep en 10 vrouwen in de afwachtgroep hadden als enige inclusiecriterium een afbuigende groei. 306 (95.6%) vrouwen uit de inleidgroep werden daadwerkelijk ingeleid, resulterend in een gemiddeld interval tussen randomisatie en start van de baring van 0.9 dagen (interquartile range(IQR) 0.7 tot 1.7). In de afwachtgroep bedroeg dit interval gemiddeld 10.4 dagen (IQR 5.6 tot 16.0). In de afwachtgroep werden 166 (50.6%) vrouwen uiteindelijk ingeleid. 45 (14.0%) moeders in de inleidgroep en 45 (13.7%) in de afwachtgroep (verschil 0.3%, 95% BI -5.0% tot 5.6%) kregen een sectio caesarea. Een vrouw (0.3%) uit de inleidgroep stierf 10 dagen na de bevalling. Zij beviel vaginaal na een spontane start van een gezond kind bij 38+4 dagen. Obductie leverde geen duidelijke verklaring voor deze sterfte en werd uitgeboekt als serieuze complicatie, niet gerelateerd aan de studie. In de afwachtgroep was geen maternale sterfte. Alle andere maternale uitkomsten waren vergelijkbaar.

In geen van beide groepen was er sprake van perinatale sterfte.[17] (5.3%) neonaten in de inleidgroep en 20 (6.1%) in de afwachtgroep hadden een slechte uitkomst (verschil 0.8%, 95% BI - 4.3% tot 2.8%). Op geen van de onderdelen van de samengestelde primaire uitkomst (5 min Apgar, navelstreng pH of NICU opname) vonden we verschillen tussen de twee groepen. Kinderen in de inleidgroep waren

gemiddeld 130 gram lichter en 10 dagen jonger (2420 gram versus 2550 gram; verschil 130 g, 95% BI 188 g tot 71 g; P<0.001). Desondanks was het percentage ernstig groeivertraagde kinderen (<P 2.3) groter na een afwachtend beleid (100 (31%) v 40 (13%); verschil 18.1%, 95% BI 24.3% tot 12.0%; P<0.001). Significant meer kinderen uit de inleidgroep werden op de kinderafdeling opgenomen (155 (48.4%) v 118 (36.3%); verschil 12.1%, 95% BI 4.6% tot 19.7%; P<0.05).

We concludeerden dat inleiden van de baring en een afwachtend beleid bij vrouwen met een verdenking op a terme IUGR vergelijkbare foetale en maternale uitkomsten geeft. Dit betekent dat beide strategieën veilig zijn. Echter, aangezien er geen verhoogd risico op een kunstverlossing of sectio caesarea is na inleiding, is het aannemelijk om een beleid van inleiden te kiezen om een eventuele vruchtdood te voorkomen. Door de baring in te leiden kan de foetus die niet meer groeit uit zijn ondervoede omgeving bevrijd worden.

Hoofdstuk 5

In dit hoofdstuk wordt de neonatale morbiditeit in detail vergeleken tussen de beide strategieën. Aanleiding tot deze studie was het significante verschil dat we vonden in het aantal opnames op de kinderafdeling tussen de beide groepen, ten nadele van inleiden. We vroegen ons af of dit alleen te wijten was aan het feit dat de kinderen gemiddeld 10 dagen jonger en 130 gram lichter waren en misschien vanwege ziekenhuis protocol werden opgenomen. Waren deze kinderen nu echt zieker, of waren de kinderen die opgenomen werden na een expectatief beleid misschien wel zieker, mede omdat ze ernstiger groeivertraagd raakten? Om dit objectief te vergelijken werd van alle opgenomen kinderen de gevalideerde morbidity assessment index for newborns (MAIN) score bepaald. Deze score geeft een cijfermatige indexering van vroege perinatale uitkomsten van obstetrisch beleid van kinderen die geboren zijn na 28 weken. The MAIN score kon van 308 ingeleide vrouwen en van 315 expectatieve groep vrouwen berekend worden. Er werd geen verschil in de MAIN score categorieën (geen/minimale, milde, middelmatige en ernstige morbiditeit) gevonden tussen de groepen. Morbiditeit bij a terme groei-

vertraging is relatief mild en vergelijkbaar voor zowel inleiding als een afwachtend beleid. Het item hyperbilirubinemia >220 mmol/L of de noodzaak tot fototherapie werd significant vaker gescoord na inleiding van de baring (n=32 (10.4%) voor inleiding versus n=18 (5.7%) voor een afwachtend beleid; verschil 4.7%, 95% CI 0.4% tot 8.9%, p<0.05). Vervolgens werden de twee groepen op de uitkomsten neonatale opnames, een positieve MAIN score en een samengestelde slechte uitkomst vergeleken in vrouwen gerandomiseerd voor 38 weken, vanaf 38 tot 40 weken en na 40 weken. We vonden dat in dat geval alleen het percentage opnames op de kinderafdeling significant hoger was na een inleiding voor 38 weken; 125 (61%) opnames na een inleiding versus 92 (44%) na een afwachtend beleid; verschil 16%, 95% CI 6.7% tot 26%, p=0.001).

We concludeerden dat het overschot aan opnames op de kinderafdeling na een inleiding in de DIGITAT studie een bijverschijnsel is van relatieve late prematuriteit en geen kenmerk van ernstige neonatale morbiditeit. Wanneer men kiest voor een inleiding van de baring bij IUGR rond de a terme leeftijd, dan heeft het de voorkeur om dit uit te stellen tot na 38 weken zwangerschap. Op die manier kunnen de complicaties ten gevolge van relatieve prematuriteit beperkt worden, mits moeder en kind strikt bewaakt worden.

Hoofdstuk 6

In hoofdstuk 6 worden de resultaten van niet-gerandomiseerde vrouwen beschreven. Alle vrouwen die voor de DIGITAT studie in aanmerking kwamen, maar die niet gerandomiseerd wilden worden, werden gevraagd om toestemming voor het prospectief volgen van hun medische gegevens. Precies dezelfde data werden verzameld en in de data-base ingevoerd. Dezelfde primaire uitkomsten als van de gerandomiseerde vrouwen werden geanalyseerd. 452 vrouwen gaven toestemming om als weigeraar vervolgd te worden. Deze weigeraars waren ouder, hadden een lagere body mass index (BMI), rookten minder en waren hoger opgeleid. Bij 37 (6%) van de kinderen van gerandomiseerde deelnemers versus 32 (8%) kinderen van weigeraars (gecorrigeerde verschil -2.0%, 95% BI -5.2% tot 1.1%) was er sprake van een slechte uitkomst. 3 (0.7%) kinderen van weigeraars stierven (2 intra-ute-

riene vruchtdoden en 1 neonatale sterfte), terwijl er in de gerandomiseerde groep geen een kind stierf (aangepaste verschil -0.7%, 95% BI -1.4% tot 0.1%, p=0.06). 90 (14%) gerandomiseerde vrouwen versus 71 (16%) weigeraars (aangepast verschil -2.8%, 95% BI -7.5% tot 1.8%) ondergingen een sectio caesarea. In bijna alle vergelijkingen was er een trend naar betere uitkomsten onder de gerandomiseerde deelneemsters aan de DIGITAT studie. Na correctie voor verschillende basis karakteristieken zoals maternale leeftijd, roken, BMI, opleiding en hypertensieve aandoeningen was het aangepaste risicoverschil en het 95% betrouwbaarheidsinterval voor perinatale sterfte -0.5% (95% BI -1.4% tot 0.4%, p=0.27). Concluderend vonden we dat, zelfs na correctie voor basis karakteristieken, vrouwen die deelname weigerden neigden naar slechtere uitkomsten. Meedoen aan een studie naar a terme groeivertraging had de deelneemsters geen nadeel opgeleverd. Deze bevinding kan helpen bij het rekruteren van vrouwen voor gerandomiseerde studies.

Hoofdstuk 7

Hoofdstuk 7 geeft de resultaten weer van de maternale gezondheidsgerelateerde kwaliteit van leven (HR-QoL) na inleiding van de baring danwel na een expectatief beleid van vrouwen met een groeivertraagde foetus. Zowel gerandomiseerde vrouwen, als weigeraars werden gevraagd aan de HR-QoL studie mee te doen. De vrouwen werden gevraagd om gevalideerde HR-QoL vragenlijsten in te vullen; de Short Form (SF-36), European Quality of Life (EuroQoL 6D3L), Hospital Anxiety and Depression scale (HADS), en Symptom Check List (SCL-90). De vragenlijsten werden bij inclusie, 6 weken post partum en 6 maanden post partum ingevuld. 361 gerandomiseerde en 198 weigeraars werden geanalyseerd. Er werden geen klinische relevante verschillen gevonden tussen inleiden of afwachten in de groepen 6 weken na de bevalling, noch na 6 maanden. Dit gold voor alle verschillende vragenlijsten. De (PhysicalComponentScore (PCS) en de MentalComponentScore (MCS) van de SF-36 waren bij inclusie lager ten opzichte van de algemene nedelandse populatie. De PCS verbeterde na verloop van tijd, maar de MCS bleef verlaagd na 6 maanden. De belangrijkste conclusie was dat inleiden van de baring geen effect heeft op de lange termijn HR-QoL.

Hoofdstuk 8

Nadat we equivalentie op neonatale en maternale uitkomsten, operatieve ingrepen en kwaliteit van leven hadden aangetoond werden de kosten van de twee strategieën vergeleken. Vanuit een gezondheidsperspectief werden de medische kosten berekend die gemaakt werden vanaf het moment van inclusie tot aan het ontslag uit het ziekenhuis na de bevalling. Er werd een onderscheid gemaakt tussen 3 fases: ante partum kosten (vanaf randomisatie tot de bevalling), kosten gerelateerd aan de bevalling, en post partum kosten (vanaf geboorte tot ontslag uit het ziekenhuis). Gegevens over de volgende medische kosten werden verzameld: maternale en neonatale opnames, manier van bevallen, polikliniekbezoeken, medicatie, maternaal bloedonderzoek, cardiotocografieën (CTGs) en foetale echografieën. Een afwachtend beleid genereerde ante partum meer kosten, voornamelijk door een langere ziekenhuisopname voor de bevalling voor foetale en maternale bewaking. In de fase van de bevalling en in de post partum fase genereerde de inleidgroep meer medische kosten door langere opname op de verloskamers en vanwege meer neonatale opnames post partum. In totaal genereerde de beide strategieën vergelijkbare kosten: in de inleidgroep gemiddeld € 7,106 per patiënt en € 6,995 per patiënt in de afwachtgroep, met een gemiddeld verschil van € 111 (95% BI: - € 1,296 tot € 1,641). We concludeerden dat een strategie van inleiden van de baring en een afwachtend beleid bij verdenking op a terme groeivertraging vergelijkbare kosten genereert.

Hoofdstuk 9

Op 2 jarige leeftijd werd de lange termijn gedragsneurologische ontwikkeling van de kinderen geanalyseerd. Deze resultaten worden in hoofdstuk 9 gepresenteerd. Op 2 jarige leeftijd werden de Ages and Stages Questionnaire (ASQ) en de Child Behaviour Check List (CBCL) aan ouders die deelnamen aan de DIGITAT studie verstuurd. De Ages and Stages Questionnaire is een vragenlijst die screent op neurologische ontwikkelingsstoornissen. De CBCL vragenlijst bestaat uit 100 items die betrekking hebben op gedragsproblemen van kinderen. Uit deze 100 items kan een totale score berekend worden. 582 (89.5%) van de 650 ouders werden bena-

derd voor het invullen van de lijsten, met een respons van 50%. Van deze kinderen had 27% een abnormale score volgens de ASQ and 13 % volgens de CBCL. Resultaten van de ASQ en de CBCL waren voor inleiding van de baring en een expectatief beleid vergelijkbaar. Een zeer laag geboortegewicht (<P2.3), een positieve morbidity assessment index (MAIN score) en een opname op de kinderafdeling verhoogden de kans op een abnormale score op de ASQ, maar niet op de CBCL. Met deze secundaire lange termijn analyse toonden we aan dat er geen verschil was in (gedrags)neurologische ontwikkeling op 2 jarige leeftijd tussen de beide strategieën.

Hoofdstuk 10

We toonden aan dat de medische uitkomsten, de maternale QoL, de kosten en de gedragsneurologische ontwikkeling van de kinderen op 2 jarige leeftijd gelijk waren. Dat maakt de voorkeur die vrouwen hebben voor een van beide strategieën nog interessanter. Om inzicht te krijgen in hoe vrouwen met een intra-uteriene groeivertraging a terme verschillende obstetrische uitkomsten beoordelen, vergeleken we inleiding van de baring met een expectatief beleid door de DIGITAT studie resultaten en de preferenties van deze vrouwen te integreren. We gebruikten verschillende scenario`s (zogenaamde 'vignettes'), die vijf factoren omvatten (zogenaamde 'attributen') die door 24 deelnemende vrouwen beoordeeld werden. Er werden twee waarderingsmethoden gebruikt; de discrete choice experiment (DCE) en een visual analogue scale (VAS). Deze uitkomsten werden gecombineerd met de uitkomsten van de trial en zo werd er een gemiddelde uitkomst voor beide strategieën berekend. Bij het gebruik van de DCE zagen we geen voorkeur voor een van beide strategieën. Bij het gebruik van de VAS zagen we wel een voorkeur voor een expectatief beleid. Echter aangezien de DCE in het algemeen wordt beschouwd als een superieure methode werden de resultaten van de DCE aangehouden. De conclusie was dat er geen voorkeur is voor een inleiding, danwel voor een afwachtend beleid bij a terme groeivertraging, hetgeen een weerspiegeling is van de primaire en secundaire uitkomsten van de DIGITAT studie.

Hoofdstuk 11

We beschrijven hier de resultaten van een cohort kinderen met een geboortegewicht onder de 10de percentiel (=geïdentificeerd), bij wie er voor de geboorte een vermoeden was op groeivertraging a terme vergeleken met kinderen die pas na de geboorte als te klein geïdentificeerd werden (=niet geïdentificeerd). Alle a terme eenlingen geboren tussen 01-01-2006 and 03-31-2008 met een geboorte gewicht <P10 geboren in de Parkstad regio (Heerlen) werden bekeken.
Wanneer er duidelijk in de status van de zwangeren werd geschreven dat er een vermoeden was op groeivertraging werden de kinderen als geïdentificeerd te klein (groeivertraagd) beschouwd, bij de overige kinderen werd de groeivertraging als niet-geïdentificeerd beschouwd. Foetale bewaking in de geïdentificeerde groep bestond uit foetale echografie met wekelijks meten van de foeto-placentaire Dopplersnelheid, tweewekelijkse CTG`s of frequentere CTG`s afhankelijk van de ernst van de groeivertraging. De primaire uitkomst was een slechte neonatale uitkomst gedefinieerd als een samengestelde maat voor intra-uteriene vruchtdood, een Apgar <7 na 5 minuten, of een arteriële navelstreng pH onder de 7.05. Neonatale medium care unit (NMCU) opname langer dan 7 dagen was een secundaire uitkomst. 430 vrouwen werden in de studie geïncludeerd; in totaal werd 36.7% als te klein geïdentificeerd. In deze geïdentificeerde groep was zowel de amenorrhoeaduur als het gemiddelde geboorte gewicht lager, terwijl de maternale morbiditeit hoger was. Het aantal inleidingen van de baring en electieve sectio caesarea was significant hoger ten opzichte van de niet- geïdentificeerde groep. De totale perinatale sterfte was 2.1%. Het ongecorrigeerde odds ratio (OR) voor slechte uitkomst voor geïdentificeerde versus niet-geïdentificeerde kleine kinderen a terme bedroeg 0.40 (95% BI 0.16-1.02, p=0.056). Na correctie voor geboorte gewicht en hypertensieve aandoeningen bleek ante partum identificatie van te kleine kinderen het risico op een slechte uitkomst significant te verlagen (OR 0.28, 95%BI 0.10-0.79, p= 0.016). Concluderen leidt identificatie van te kleine kinderen tot een actiever beleid met als gevolg betere neonatale uitkomsten.

Hoofdstuk 12

bevat de discussie van dit proefschrift. Hierin worden de belangrijkste bevindingen van de DIGITAT trial en andere (secundaire) studies benoemd:

- In een retrospectief Nederlands cohort van te kleine kinderen (geboorte gewicht onder de P10) is inleiding van de baring na 36 weken geassocieerd met een hogere kans op vaginale kunstverlossingen en sectio caesarea, zonder verbetering van de neonatale uitkomsten.
- De DIGITAT studie, bron van dit proefschrift, liet vergelijkbare neonatale en maternale uitkomsten zien wanneer inleiding van de baring vergeleken werd met een expectatief beleid. Beide strategieën zijn veilig in geval van verdenking op IUGR a terme.
- In deze prospectieve studie leidde inleiding van de baring niet tot een hoger sectio percentage, noch tot een hoger aantal vaginale kunstverlossingen.
- Ook al zijn beide strategieën veilig, toch is het redelijk de baring in te leiden om een eventuele vruchtdood in geval van a terme groeivertraging te voorkomen.
- Meer kinderen worden opgenomen op de kinderafdeling na een strategie van inleiden van de baring.
- Na een afwachtend beleid wordt het percentage kinderen met een ernstige groeivertraging (<P2.3) groter.
- De MAIN score was vergelijkbaar voor kinderen geboren na inleiding en geboren na een afwachtend beleid. Kinderen geboren voor 38 weken hadden vaker een positieve MAIN score vergeleken met kinderen geboren na 38 weken. Zolang de maternale en foetale conditie het toelaten is het wenselijk om een inleiding van de baring bij a terme groeivertraging uit te stellen tot na 38 weken. Hiermee kunnen de gevolgen van relatieve prematuriteit door een relatief vroege inleiding beperkt worden.
- We lieten zien dat het mee doen aan een gerandomiseerde studie naar a terme groeivertraging geen nadelige gevolgen heeft voor de maternale en neonatale uitkomsten.
- Inleiden van de baring bij a terme groeivertraging heeft geen effect op de maternale gezondheidsgerelateerde kwaliteit van leven.

- Vanuit een gezondheidsoogpunt genereren inleiden van de baring en een expectatief beleid bij a terme IUGR vergelijkbare kosten.
- Vrouwen met een a terme groeivertraging hebben een gelijke voorkeur voor inleiding of afwachten.
- Op 2 jarige leeftijd is er geen verschil in (gedrags)neurologische ontwikkeling tussen inleiden of afwachten. Ernstige groeivertraging (<P2.3) en opname op de kinderafdeling zijn de belangrijkste voorspellers voor problemen in de neurologische ontwikkeling (gemeten met de Ages and Stages Questionnair) op 2 jarige leeftijd.
- Ante partum verdenking op groeivertraging leidt tot een actiever beleid resulterend in betere neonatale uitkomsten bij a terme groeivertraging ten opzichte van kinderen die pas na de geboorte te klein blijken te zijn.

Conclusie

Zowel inleiden van de baring als een expectatief beleid, met foetale en maternale bewaking, zijn veilige strategieën in a terme groeivertraging.
Directe neonatale en maternale uitkomsten, het percentage kunstverlossingen en sectio caesarea, de maternale kwaliteit van leven, de kosten, als ook de (gedrags)neurologische ontwikkeling van de kinderen op 2 jarige leeftijd zijn gelijk. Het is echter redelijk om de baring in te leiden na 38 weken zwangerschapsduur om een eventuele vruchtdood te voorkomen, mits de maternale en foetale conditie dit toestaan. In theorie zou door bij 10 vrouwen de inleiding tot na 38 weken uit te stellen 1 neonatale opname door gevolgen van relatieve late prematuriteit vermeden kunnen worden. Verder uitstel van de baring maakt de kans op ernstigere groeivertraging (<P2.3) alleen maar groter. Het blijft een uitdaging om echte groeivertraging a terme op te sporen om zo de kinderen die het hoogste risico op morbiditeit en mortaliteit hebben te identificeren. Het individualiseren van de groeicurves (eigen groeipotentie bepalen) en ontwikkelen van diagnostische risicoscores, integratie van Doppler metingen in de navelstreng en arteria cerebri

media vormen een opzet naar toekomstige studies. Door het ontwikkelen van behandel-selectie-markers, zogenaamde treatment selection markers, zouden we kunnen evalueren of het mogelijk is de juiste zorg voor de individuele patiënt in geval van a terme groeivertraging te leveren: inleiden van de baring of een expectatief beleid met bewaking van moeder en kind.

Appendices

Collaborators to the DIGITAT study

In addition to the authors in the manuscripts of this thesis, the following Dutch institutions and gynecologists participated in the DIGITAT study:

P J A van der Lans (Twenteborg Hospital, Almelo); G Kleiverda (Flevo Hospital, Almere); M H B Heres (Sint Lucas Andreas, Amsterdam); M Wouters (VU Medical Centre, Amsterdam); A J M Huisjes (Gelre Hospital, Apeldoorn); M J Noordam (Lievensberg Hospital, Bergen op Zoom); D J Bekedam (Onze Lieve Vrouwe Gasthuis, Amsterdam), D N M Papastonis (Amphia Hospital, Breda); P C M van der Salm (Meander Medical Center, Amersfoort), R J P Rijnders (Jeroen Bosch Hospital, Den Bosch); W J van Wijngaarden (Bronovo Hospital, Den Haag); M E van Huizen (Haga Leyenburg, Den Haag); J Lind (Medical Center Haaglanden, The Hague); R H Stigter (Deventer Hospital, Deventer); B M C Akerboom (Albert Schweizer Hospital, Dordrecht); J M Burggraaff (Scheper Hospital, Emmen); A J van Loon (Martini Hospital, Groningen); P J M Pernet (Kennermer Gasthuis, Haarlem); A Lub (Spaarne Hospital, Haarlem); D Perquin (Medical Centre Leeuwarden, Leeuwarden); F J A Copraij (Diaconessenhuis, Leiden); L S M Ribbert (Sint Antonius Hospital, Nieuwegein); J M J Sporken (Canisius-Wilhelmina Hospital, Nijmegen); J W de Leeuw (Ikazia Hospital, Rotterdam); T H M Hasaart (Catharina Hospital, Eindhoven); PE van der Moer (Maasstad Hospital, Rotterdam); N van Gemund (St Franciscus Gasthuis, Rotterdam); R Aardenburg (Maasland Hospital, Sittard); C M van Oirschot (St Elisabeth Hospital, Tilburg); A P Drogtrop (Twee Steden Hospital, Tilburg); J P R Doornbos (Zaans Medical Centre, Zaandam); A A van Ginkel (Alysis Zorggroep, Zevenaar); and J van Eyck (Isala Hospital, Zwolle).

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Publications

Boers KE, van Wyk L, van der Post JAM, Bremer HA, Kwee A, Delemarre FMC, van Pampus MG, Bloemenkamp KWM, Roumen FJME, van Lith JMM, Mol BWJ, Thornton JG, le Cessie S, Scherjon SA for the DIGITAT study group. Comparison of participants and non-participants in a trial of induction versus expectant monitoring for intrauterine growth restriction at term (the DIGITAT trial). *Submitted BJOG.*

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Curriculum Vitae

Kim Esther Boers werd op 26 april 1972 geboren in Rotterdam. Na haar lagere schooltijd op de Rotterdamse Schoolvereniging, behaalde zij in 1990 haar eindexamen aan het Erasmiaans Gymnasium te Rotterdam. In datzelfde jaar begon zij aan haar studie Geneeskunde aan de Rijksuniversiteit Leiden. Zij werkte tijdens haar studie bij de stichting Eurotransplant Leiden. In 1998 behaalde zij haar artsexamen en ging hierna als Agnio Chirurgie in het Diaconessenhuis Leiden aan het werk. In 1999 besloot zij haar toekomst in de Gynaecologie en Verloskunde te vervolgen en werd Agnio in het Reinier de Graaf ziekenhuis te Delft bij de toenmalige opleider Dr. Johan Kuijpers. In 2001 ontmoette zij Dr. Sicco Scherjon, die plannen had liggen voor thuismonitoring van vrouwen met complicaties in hun zwangerschap. Vervolgens zette zij als Agnio Gynaecologie en Verloskunde in het Leids Universitair Medisch Centrum het "Thuisproject hoog-risico zwangeren" voor de regio Zuid-Holland Noord op, een samenwerkingsverband tussen het Diaconessenhuis Leiden, het Leids Universitair Medisch Centrum en het Bronovo ziekenhuis Den Haag. Van 2002 tot 2008 volgde zij haar opleiding tot gynaecoloog in het Leidse cluster met als academisch opleider professor H.H.H. Kanhai en als perifeer opleider Dr. R.A. Verwey in het Bronovo ziekenhuis en later C.A.G. Holleboom. Na een jaar verdieping in de Verloskunde met professor J.M.M. van Lith als hoofd van de afdeling werkt zij sinds 2009 als algemeen gynaecoloog met aandachtsgebied perinatologie in de maatschap van het Bronovo ziekenhuis, waar zij haar toenmalige opleider Robert Verwey opvolgde. In 2004 startte zij als onderzoeker met de DIGITAT-studie.

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