

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/18948> holds various files of this Leiden University dissertation.

Author: Boers, Kim Esther

Title: Strategies in intrauterine growth restriction at term

Issue Date: 2012-05-16

Chapter 3

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



KE Boers
D Bijlenga
BWJ Mol
S LeCessie
E Birnie
MG van Pampus
RH Stigter
KWM Bloemenkamp
CA van Meir
JAM van der Post
DJ Bekedam
LSM Ribbert
AP Drogdrop
PCM van der Salm
AJM Huisjes
C Willekes
FJME Roumen
HCJ Scheepers
K de Boer
JJ Duvekot
JG Thornton
SA Scherjon

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 mortality²⁴ 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 apparent³⁷, 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 proceeded 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 be 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 umbilicalis, 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

Reference List

- (1) Clausson B, Cnattingius S, Axelsson O. Preterm and term births of small for gestational age infants: a population-based study of risk factors among nulliparous women. *Br J Obstet Gynaecol* 1998; 105(9):1011-1017.
- (2) Balcazar H, Keefer L, Chard T. Use of anthropometric indicators and maternal risk factors to evaluate intrauterine growth retardation in infants weighing more than 2500 grams at birth. *Early Hum Dev* 1994; 36(3):147-155.
- (3) Chang TC, Robson SC, Spencer JA, Gallivan S. Prediction of perinatal morbidity at term in small fetuses: comparison of fetal growth and Doppler ultrasound. *Br J Obstet Gynaecol* 1994; 101(5):422-427.
- (4) Boulet SL, Alexander GR, Salihu HM, Kirby RS, Carlo WA. Fetal growth risk curves: defining levels of fetal growth restriction by neonatal death risk. *Am J Obstet Gynecol* 2006; 195(6):1571-1577.
- (5) Dijkhoorn MJ, Visser GH, Touwen BC, Huisjes HJ. Apgar score, meconium and acidaemia at birth in small-for-gestational age infants born at term, and their relation to neonatal neurological morbidity. *Br J Obstet Gynaecol* 1987; 94(9):873-879.
- (6) Low JA, Galbraith RS, Muir D, Killen H, Karchmar J, Campbell D. Intrauterine growth retardation: a preliminary report of long-term morbidity. *Am J Obstet Gynecol* 1978; 130(5):534-545.
- (7) Soothill PW, Ajayi RA, Campbell S, Nicolaidis KH. Prediction of morbidity in small and normally grown fetuses by fetal heart rate variability, biophysical profile score and umbilical artery Doppler studies. *Br J Obstet Gynaecol* 1993; 100(8):742-745.
- (8) Harvey D, Prince J, Bunton J, Parkinson C, Campbell S. Abilities of children who were small-for-gestational-age babies. *Pediatrics* 1982; 69(3):296-300.
- (9) Paz I, Gale R, Laor A, Danon YL, Stevenson DK, Seidman DS. The cognitive outcome of full-term small for gestational age infants at late adolescence. *Obstet Gynecol* 1995; 85(3):452-456.
- (10) Blair E, Stanley F. Intrauterine growth and spastic cerebral palsy. I. Association with birth weight for gestational age. *Am J Obstet Gynecol* 1990; 162(1):229-237.
- (11) Chard T, Yoong A, Macintosh M. The myth of fetal growth retardation at term. *Br J Obstet Gynaecol* 1993; 100(12):1076-1081.
- (12) Battaglia FC. Intrauterine growth retardation. *Am J Obstet Gynecol* 1970; 106(7):1103-1114.
- (13) Doctor BA, O'Riordan MA, Kirchner HL, Shah D, Hack M. Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. *Am J Obstet Gynecol* 2001; 185(3):652-659.
- (14) Minior VK, Divon MY. Fetal growth restriction at term: myth or reality? *Obstet Gynecol* 1998; 92(1):57-60.
- (15) Deter RL, Harrist RB, Hill RM. Neonatal growth assessment score: a new approach to the detection of intrauterine growth retardation in the newborn. *Am J Obstet Gynecol* 1990; 162(4):1030-1036.
- (16) Drooger JC, Troe JW, Borsboom GJ, Hofman A, Mackenbach JP, Moll HA et al. Ethnic differences in prenatal growth and the association with maternal and fetal characteristics. *Ultrasound Obstet Gynecol* 2005; 26(2):115-122.
- (17) Deter RL. Individualized growth assessment: evaluation of growth using each fetus as its own control. *Semin Perinatol* 2004; 28(1):23-32.
- (18) Mongelli M, Gardosi J. Reduction of false-positive diagnosis of fetal growth restriction by application of customized fetal growth standards. *Obstet Gynecol* 1996; 88(5):844-848.
- (19) Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. *Lancet* 1992; 339(8788):283-287.
- (20) Larciprete G, Valensise H, Di PG, Vasapollo B, Casalino B, Arduini D et al. Intrauterine growth restriction and fetal body composition. *Ultrasound Obstet Gynecol* 2005; 26(3):258-262.
- (21) Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J et al. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. *Am J Obstet Gynecol* 1999; 180(3 Pt 1):750-756.
- (22) Walther FJ, Ramaekers LH. The ponderal index as a measure of the nutritional status at birth and its relation to some aspects of neonatal morbidity. *J Perinat Med* 1982; 10(1):42-47.
- (23) Ott WJ. Small for gestational age fetus and neonatal outcome: reevaluation of the relationship. *Am J Perinatol* 1995; 12(6):396-400.

- (24) Myers SA, Ferguson R. A population study of the relationship between fetal death and altered fetal growth. *Obstet Gynecol* 1989; 74(3 Pt 1):325-331.
- (25) Villar J, de OM, Kestler E, Bolanos F, Cerezo R, Bernedes H. The differential neonatal morbidity of the intrauterine growth retardation syndrome. *Am J Obstet Gynecol* 1990; 163(1 Pt 1):151-157.
- (26) Balcazar H, Haas J. Classification schemes of small-for-gestational age and type of intrauterine growth retardation and its implications to early neonatal mortality. *Early Hum Dev* 1990; 24(3):219-230.
- (27) Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The "brain-sparing" effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. *Am J Obstet Gynecol* 1993; 169(1):169-175.
- (28) Valcamonico A, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F et al. Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. *Am J Obstet Gynecol* 1994; 170(3):796-801.
- (29) Steiner H, Staudach A, Spitzer D, Schaffer KH, Gregg A, Weiner CP. Growth deficient fetuses with absent or reversed umbilical artery end-diastolic flow are metabolically compromised. *Early Hum Dev* 1995; 41(1):1-9.
- (30) Li H, Gudmundsson S, Olofsson P. Prospect for vaginal delivery of growth restricted fetuses with abnormal umbilical artery blood flow. *Acta Obstet Gynecol Scand* 2003; 82(9):828-833.
- (31) Fong KW, Ohlsson A, Hannah ME, Grisaru S, Kingdom J, Cohen H et al. Prediction of perinatal outcome in fetuses suspected to have intrauterine growth restriction: Doppler US study of fetal cerebral, renal, and umbilical arteries. *Radiology* 1999; 213(3):681-689.
- (32) Watt J. Small-for-gestational age infants: perinatal, physical and social factors in the first year of life. *N Z Med J* 1989; 102(875):469-472.
- (33) Walther FJ. Growth and development of term disproportionate small-for-gestational age infants at the age of 7 years. *Early Hum Dev* 1988; 18(1):1-11.
- (34) Westwood M, Kramer MS, Munz D, Lovett JM, Watters GV. Growth and development of full-term nonasphyxiated small-for-gestational-age newborns: follow-up through adolescence. *Pediatrics* 1983; 71(3):376-382.
- (35) Low JA, Handley-Derry MH, Burke SO, Peters RD, Pater EA, Killen HL et al. Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. *Am J Obstet Gynecol* 1992; 167(6):1499-1505.
- (36) Hill RM, Verniaud WM, Deter RL, Tennyson LM, Rettig GM, Zion TE et al. The effect of intrauterine malnutrition on the term infant. A 14-year progressive study. *Acta Paediatr Scand* 1984; 73(4):482-487.
- (37) Parkinson CE, Scrivener R, Graves L, Bunton J, Harvey D. Behavioural differences of school-age children who were small-for-dates babies. *Dev Med Child Neurol* 1986; 28(4):498-505.
- (38) Dobbing J, Sands J. Quantitative growth and development of human brain. *Arch Dis Child* 1973; 48(10):757-767.
- (39) Dobbing J, Sands J. Comparative aspects of the brain growth spurt. *Early Hum Dev* 1979; 3(1):79-83.
- (40) Skuse D, Pickles A, Wolke D, Reilly S. Postnatal growth and mental development: evidence for a "sensitive period". *J Child Psychol Psychiatry* 1994; 35(3):521-545.
- (41) Babson SG, Kangas J. Preschool intelligence of undersized term infants. *Am J Dis Child* 1969; 117(5):553-557.
- (42) Drillien CM, Thomson AJ, Burgoyne K. Low-birthweight children at early school-age: a longitudinal study. *Dev Med Child Neurol* 1980; 22(1):26-47.
- (43) Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med* 2005; 353(17):1802-1809.
- (44) Xenakis EM, Piper JM, Conway DL, Langer O. Induction of labor in the nineties: conquering the unfavorable cervix. *Obstet Gynecol* 1997; 90(2):235-239.
- (45) Larsen T, Larsen JF, Petersen S, Greisen G. Detection of small-for-gestational-age fetuses by ultrasound screening in a high risk population: a randomized controlled study. *Br J Obstet Gynaecol* 1992; 99(6):469-474.
- (46) The Netherlands Perinatal Registry Foundation. Perinatal care in the Netherlands, 2005. The Netherlands Perinatal Registry Foundation, 2008.

- (47) GRIT studygroup. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. *BJOG*. 2003;110:27-32. 1-1-2003.
- (48) Hille ET, Elbertse L, Gravenhorst JB, Brand R, Verloove-Vanhorick SP. Nonresponse bias in a follow-up study of 19-year-old adolescents born as preterm infants. *Pediatrics* 2005; 116(5):e662-e666.
- (49) McCowan LM, Harding JE, Roberts AB, Barker SE, Ford C, Stewart AW. A pilot randomized controlled trial of two regimens of fetal surveillance for small-for-gestational-age fetuses with normal results of umbilical artery doppler velocimetry. *Am J Obstet Gynecol* 2000; 182(1 Pt 1):81-86.
- (50) van den Hove MM, Willekes C, Roumen FJ, Scherjon SA. Intrauterine growth restriction at term: induction or spontaneous labour? Disproportionate intrauterine growth intervention trial at term (DIGITAT): a pilot study. *Eur J Obstet Gynecol Reprod Biol* 2006; 125(1):54-58.