Strategies in intrauterine growth restriction at term

Boers, K.E.

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.

Reference List

(1) Smith GC, Fretts RC. Stillbirth. Lancet 2007; 370(9600):1715-1725.

(2) Evers AC, Nikkels PG, Brouwers HA, Boon J, van Egmond-Linden A, Hart C et al. Substandard care in antepartum term stillbirths: prospective cohort study. Acta Obstet Gynecol Scand 2011; 90(12):1416-1422.

(3) Bukowski R. Stillbirth and fetal growth restriction. Clin Obstet Gynecol 2010; 53(3):673-680.

(4) Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birthweight and gestational age in antepartum stillbirths. Br J Obstet Gynaecol 1998; 105(5):524-530.

(5) Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ 2005; 331(7525):1113-1117.

(6) Many A, Fattal-Valevski A, Leitner Y. Neurodevelopmental and cognitive assessment of 6-year-old children born growth restricted. Int J Gynaecol Obstet 2005; 89(1):55-56.

(7) Fattal-Valevski A, Leitner Y, Kutai M, Tal-Posener E, Tomer A, Lieberman D et al. Neurodevelopmental outcome in children with intrauterine growth retardation: a 3-year follow-up. J Child Neurol 1999; 14(11):724-727.

(8) Leitner Y, Fattal-Valevski A, Geva R, Eshel R, Toledano-Alhadef H, Rotstein M et al. Neurodevelopmental outcome of children with intrauterine growth retardation: a longitudinal, 10-year prospective study. J Child Neurol 2007; 22(5):580-587.

(9) Grivell RM, Wong L, Bhatia V. Regimens of fetal surveillance for impaired fetal growth. Cochrane Database Syst Rev 2009;(1):CD007113.

(10) http://www.studies-obsgyn.nl/home/page.asp?page_id=326. 26-12-0012. 26-1-2012.

(11) 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.

(12) Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009; 374(9694):979-988.

(13) Caughey AB. Preventive induction of labor: can its use lower the cesarean delivery rate? J Womens Health (Larchmt) 2009; 18(11):1743-1745.

(14) Gulmezoglu AM, Crowther CA, Middleton P. Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database Syst Rev 2006;(4):CD004945.

(15) Lakerveld J, Ijzelenberg W, van Tulder MW, Hellemans IM, Rauwerda JA, van Rossum AC et al. Motives for (not) participating in a lifestyle intervention trial. BMC Med Res Methodol 2008; 8:17.

(16) Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 2005; 365(9453):82-93.

(17) Akobeng AK. Assessing the validity of clinical trials. J Pediatr Gastroenterol Nutr 2008; 47(3):277-282.

(18) Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". J Clin Epidemiol 2001; 54(3):217-224.

(19) McCarney R, Warner J, Iliffe S, van HR, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol 2007; 7:30.

(20) Clarke M, Loudon K. Effects on patients of their healthcare practitioner's or institution's participation in clinical trials: a systematic review. Trials 2011; 12:16.

(21) Dekkers OM, Vandenbroucke JP. [Generalizability of therapeutic trials]. Ned Tijdschr Geneeskd 2007; 151(40):2203-2206.

(22) Eixarch E, Meler E, Iraola A, Illa M, Crispi F, Hernandez-Andrade E et al. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. Ultrasound Obstet Gynecol 2008; 32(7):894-899.

(23) Bijlenga D, Koopmans CM, Birnie E, Mol BW, van der Post JA, Bloemenkamp KW et al. Health-related quality of life after induction of labor versus expectant monitoring in gestational hypertension or preeclampsia at term. Hypertens Pregnancy 2011; 30(3):260-274.

(24) Ohel G, Ruach M. Perinatal outcome of idiopathic small for gestational age pregnancies at term: the effect of antenatal diagnosis. Int J Gynaecol Obstet 1996; 55(1):29-32.
(25) Jahn A, Razum O, Berle P. Routine screening for intrauterine growth retardation in Germany: low sensitivity and questionable benefit for diagnosed cases. Acta Obstet Gynecol Scand 1998; 77(6):643-648.
(26) Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992; 339(8788):283-287.
(27) Figueras F, Figueras J, Meler E, Eixarch E, Coll O, Gratacos E et al. Customised birthweight standards accurately predict perinatal morbidity. Arch Dis Child Fetal Neonatal Ed 2007; 92(4):F277-F280.
(28) Wolf H, Schaap AH. [What is the normal fetal weight?]. Ned Tijdschr Geneeskd 2009; 153(18):844-847.
(29) Morrison JL, Duffield JA, Muhlhausler BS, Gentili S, McMillen IC. Fetal growth restriction, catch-up growth and the early origins of insulin resistance and visceral obesity. Pediatr Nephrol 2010; 25(4):669-677.
(30) Tajik P, Bossuyt PM. Genomic markers to tailor treatments: waiting or initiating? Hum Genet 2011; 130(1):15-18.