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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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.

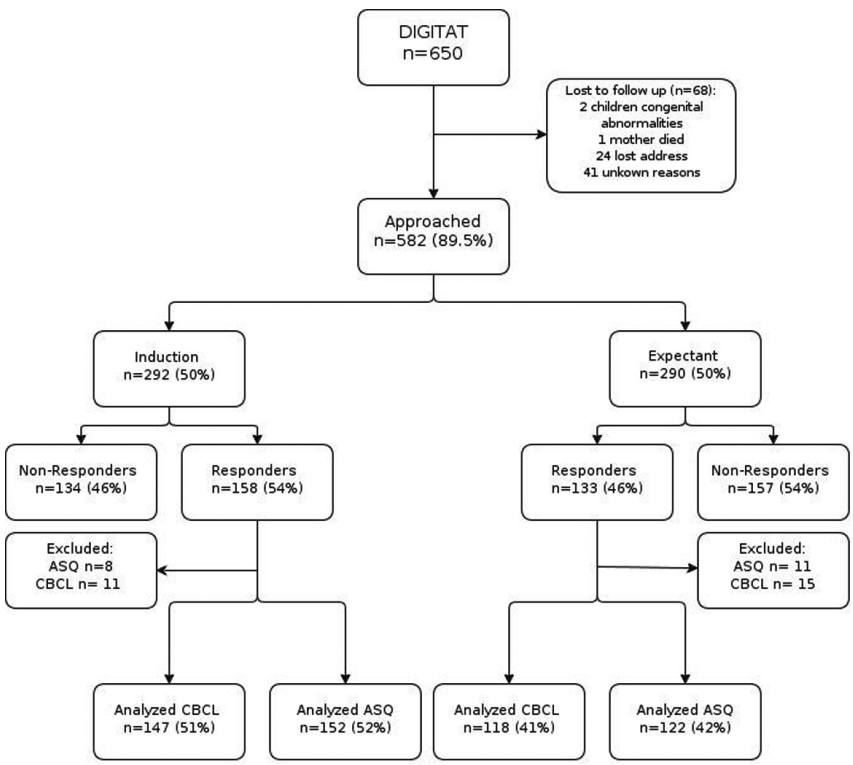

Table 1
Baseline characteristics

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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