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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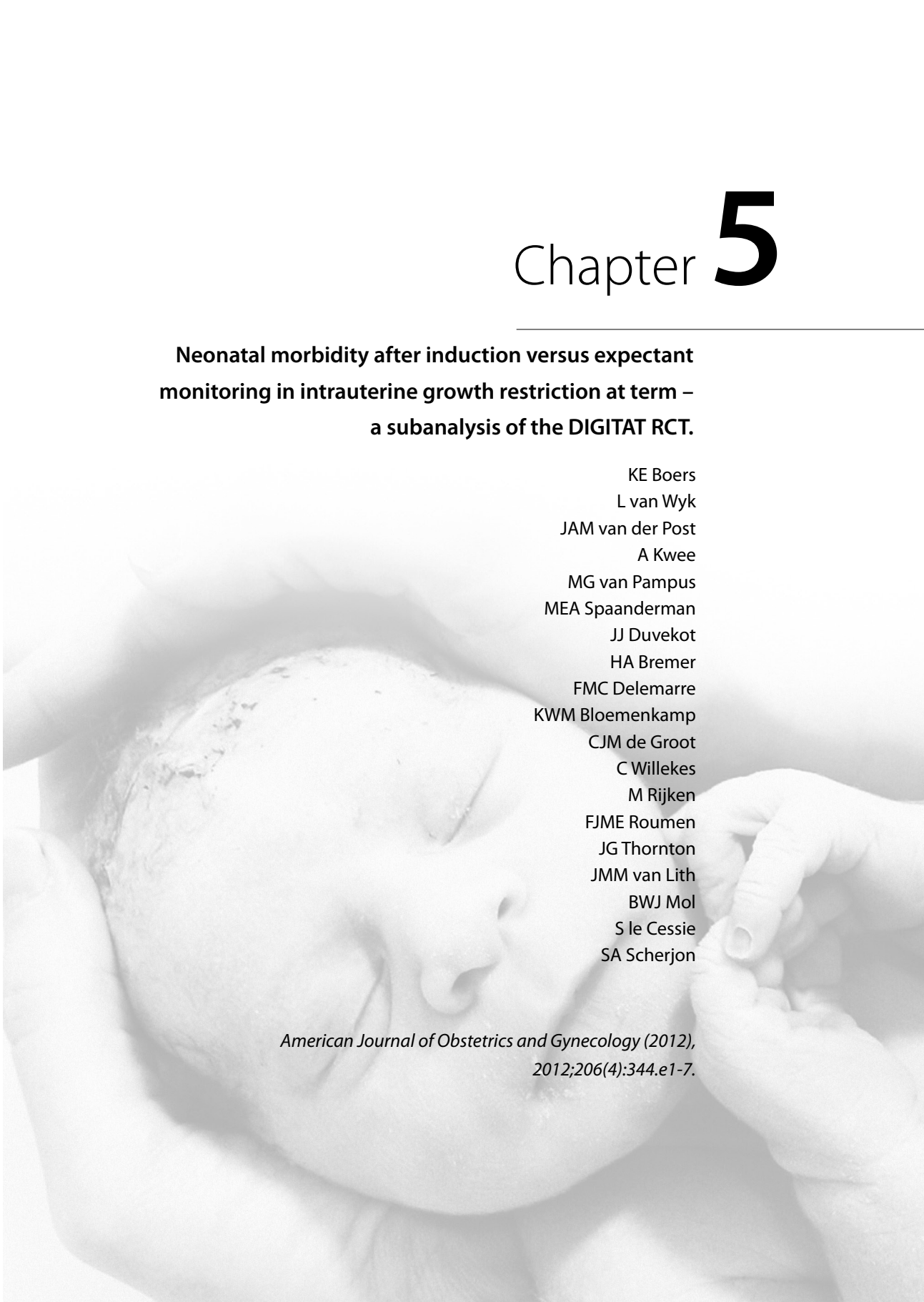

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Abstract

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.

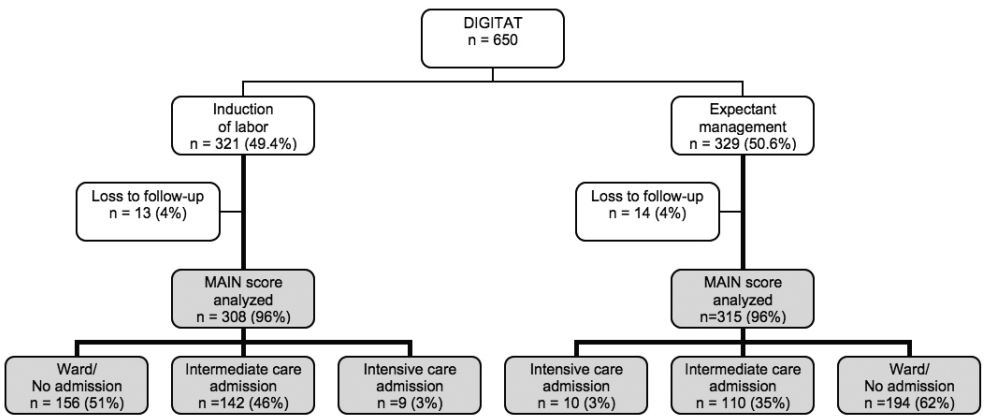
Data were analyzed according to intention-to-treat. Continuous variables were compared using Student's t-test or Fisher exact test when data were normally distributed, or the nonparametric Mann-Whitney U test for skewed data. The chi-square test was used for categorical variables. Treatment effects were 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.

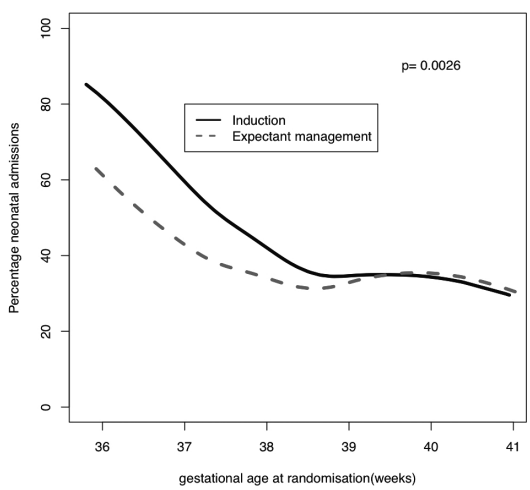
Table 3
Mean MAIN score shown for different admission categories and different growth centiles

	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

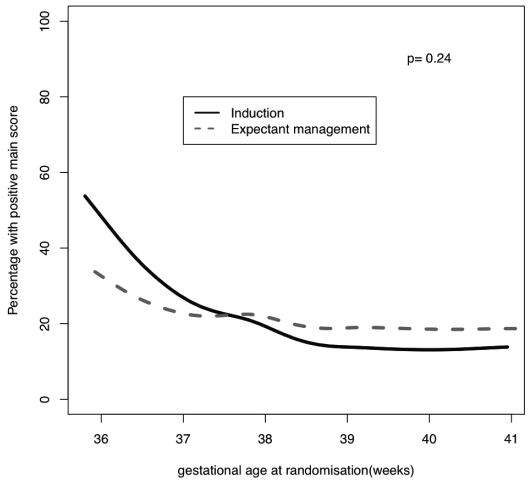
Table shows mean; median (interquartile range 25th to 75th percentile)
Data were analyzed with the Student t-test.

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).

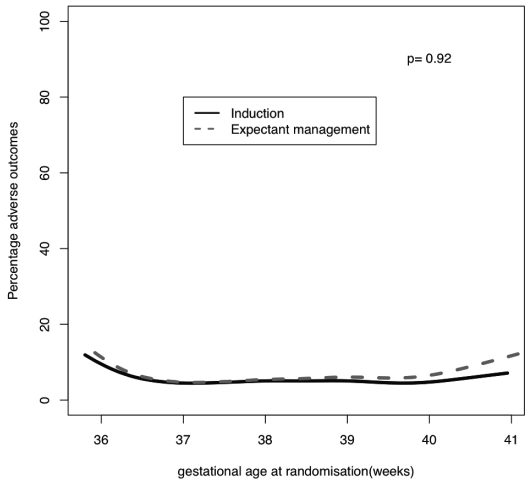
Figuur 2
Gestational age at randomization vs. percentage of neonatal admission.



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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