OBSTETRICS

Neonatal morbidity after induction vs expectant monitoring in intrauterine growth restriction at term: a subanalysis of the DIGITAT RCT

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OBJECTIVE: The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT) compared induction of labor and expectant management in suspected intrauterine growth restriction (IUGR) at term. In this subanalysis, we report neonatal morbidity between the policies based on the Morbidity Assessment Index for Newborns (MAIN).

STUDY DESIGN: We used data from the DIGITAT. For each neonate, we calculated the MAIN score, a validated outcome scale.

RESULTS: There were no differences in mean MAIN scores or in MAIN morbidity categories. We found that neonatal admissions are lower after 38 weeks' gestational age compared with 36 and 37 weeks in both groups.

CONCLUSION: 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.

Key words: Disproportionate Intrauterine Growth Intervention Trial at Term, induction of labor, intrauterine growth restriction at term, Morbidity Assessment Index for Newborns score, neonatal morbidity

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Intrauterine growth restriction (IUGR) is defined as an estimated fetal weight or an abdominal circumference below the 10th centile for gestational age.[1] Postnatally, children with a birthweight below the 10th centile are classified as small for gestational age (SGA). The latter condition is identified only 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 SGA but followed up 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 the intensive care unit did

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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% vs 36%; difference, 12%; 95% confidence interval [CI], 5–20%).

Complications of late prematurity[13,18,19] might explain this because children in the induction group were born on average 10 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 2 competing explanations because in the expectant group, more children were severely growth restricted, defined as a birthweight below the third percentile (13% vs 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 2 policies on neonatal morbidity in detail, the Morbidity Assessment Index for Newborns (MAIN) score, a validated outcome measure for neonatal morbidity, was calculated and compared.[20,21]

Materials and Methods

This is a secondary analysis of the DIGITAT. 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. 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 or an estimated fetal weight below the 10th percentile or deceleration of the fetal abdominal circumference in the third trimester.[20]

Exclusion criteria were previous cesarean section, diabetes mellitus, or gestational diabetes requiring insulin therapy, renal failure, human immunodeficiency virus seropositivity, prelabor rupture of membranes, severe preeclampsia, 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 cesarean section was performed for obstetrical indications, such as suboptimal fetal heart rate tracings, prolonged rupture of membranes, or postmaturity between T plus 7 and T plus 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 4 morbidity categories: below 150 (no/minimal morbidity), 151-500 (mild morbidity), 501-800 (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 the 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 a Student *t* test or Fisher exact test when data were normally distributed or the nonparametric Mann-Whitney *U* test for skewed data. The χ^2 test was used for categorical variables. Treatment effects were presented as difference in percentages with 95% CIs. *P* values less than .05 were considered to indicate statistical significance. If more than 5% of observations were

FIGURE 1
Flow diagram of study subjects and their admission categories

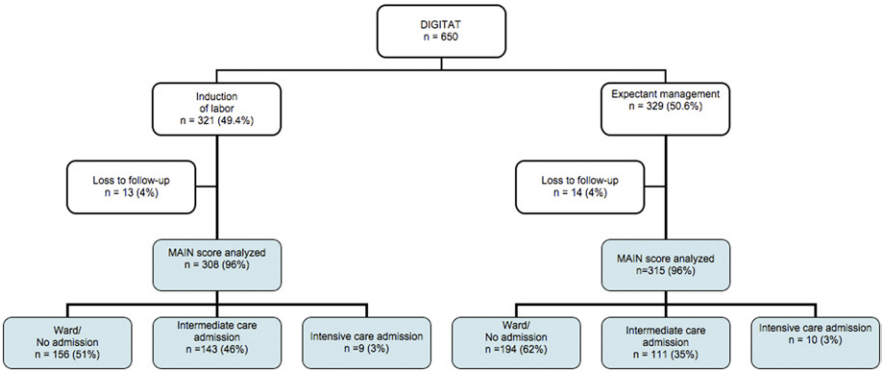

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TABLE 1
Baseline characteristics of randomized participants as well as main trial results

Characteristic	Induction of labor (n = 321)	Expectant monitoring (n = 329)	Difference in percentage or mean (95% CI)
Nulliparous	182 (56.7)	201 (61.1)	−4.4 (−12.0 to 3.2)
Maternal age, y	26.9 (23.3–31.2)	27.4 (23.3–31.4)	−0.04 (−8.6 to 7.8)
BMI at study entry[a]	21.9 (19.7–25.5)	22.2 (19.7–25.6)	−0.1 (−1.0 to 0.7)
Maternal smoking[b]	138 (46.9)	127 (40.8)	−6.1 (−1.8 to 14)
Gestational age at randomization, d	264 (258–269)	264 (258–268)	−0.7 (−2.1 to 0.7)
White[c]	254 (83.6)	253 (81.1)	−2.5 (−3.6 to 8.5)
Education			
Lower professional school	168 (52.3)	170 (51.7)	0.6 (−7.0 to 8.4)
Medium professional school	26 (8.1)	37 (11.2)	−3.1 (−7.7 to 1.4)
Unknown	127 (39.6)	122 (37.1)	−2.5 (−5.0 to 10.0)
Inclusion criteria			
Fetal abdominal circumference less than the 10th percentile	262 (81.6)	270 (82.1)	−0.5 (−6.4 to 5.5)
Estimated fetal weight less than the 10th percentile	296 (92.2)	308 (93.6)	−1.4 (−5.4 to 2.5)
Flattening of fetal abdominal circumference curve	83 (25.9)	84 (25.5)	−0.4 (−6.4 to 7.0)
Onset of labor			
Spontaneous	12 (3.7)	151 (46.0)	−42.3 (−48.1 to −36.5)
Induction	306 (95.6)	166 (50.6)	45.0 (39.2–50.9)
Elective cesarean section	2 (0.6)	11 (3.3)	−2.7−4.9 to −0.6)
Mode of delivery			
Spontaneous	249 (77.6)	257 (78.1)	0.5 (−6.9 to 5.8)
Vaginal instrumental	27 (8.4)	27 (8.2)	0.2 (−4.0 to 4.4)
Cesarean section	45 (14.0)	45 (13.7)	0.3 (−5.0 to 5.6)
Time between randomization and onset of labor, d	0.9 (0.7–1.7)	10.4 (5.6–16.0)	−9.6 (−10.8 to −8.5)[d]
Gestational age at birth, d	266 (261–271)	277 (269–283)	−9.9 (−11.3 to −8.6)[d]
Birthweight, g	2420 (2220–2660)	2550 (2255–2850)	−130 (−188 to −71)[d]
Birthweight by percentile			
Less than third percentile	40 (12.5)	100 (30.6)	−18.1 (−24.3 to −12.0)[d]
Third to fifth percentile	82 (25.5)	79 (24.2)	1.3 (−5.3 to 8.0)
Fifth to 10th percentile	88 (27.5)	62 (18.9)	8.5 (−2.0 to 14.9)
10th to 25th percentile	88 (27.4)	66 (20.2)	7.2 (0.7−13.8)
Greater than 25th percentile	23 (7.2)	20 (6.1)	−1.1 (−2.8 to 4.9)
Composite adverse neonatal outcome	17 (5.3)	20 (6.1)	−0.8 (−4.3 to 2.8)
Neonatal admission			
Intensive care	9 (2.8)	13 (4.0)	−1.2 (−4 to 1.6)
Intermediate care	155 (48.3)	118 (35.9)	12.4 (4.9–20.0)[e]
Maternal ward	89 (27.8)	116 (35.7)	−7.9 (−15 to −0.7)[e]
No admission	67 (20.9)	78 (24.0)	−3.1 (9.5–3.4)

Data were analyzed with the Student *t* test or χ^2 test. The table shows median (interquartile range 25th to 75th percentile or number [percentage]).
BMI, body mass index; *CI,* confidence interval.

[a] n = 275 for induction; n = 295 for expectant monitoring; [b] n = 294 for induction; n = 311 for expectant monitoring; [c] n = 304 for induction; n = 312 for expectant monitoring; [d] $P < .001$; [e] $P < .05$.

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TABLE 2
Distribution of MAIN score, frequently scored/relevant MAIN items, and CNM in the 2 trial groups

Morbidity or MAIN score item	Induction of labor (n = 308), n(%)	Expectant monitoring (n = 315), n (%)	Difference in percentage (95% CI)
Morbidity according to MAIN score			
No/minimal (<150)	259 (84.1)	258 (81.9)	−2.2 (−3.7 to 8.1)
Mild (151-500)	47 (15.3)	51 (16.2)	−0.9 (−6.7 to 4.8)
Moderate (501-800)	2 (0.7)	5 (1.6)	−0.9 (−2.6 to 0.7)
Severe (>800)	0 (0)	1 (0.3)	−0.3 (−0.9 to 0.3)
MAIN score item			
Serum bilirubin 251-340 μmol/L or phototherapy	32 (10.4)	18 (5.7)	4.7 (0.4–8.9)[a]
Apnea and need for oxygen[b]	2 (0.7)	5 (1.6)	−0.9 (−2.6 to 0.7)
Assisted ventilation beyond 24 h[b]	0 (0.0)	5 (1.6)	−1.6 (−3.0 to −0.2)
Cord blood pH <7.1	11 (3.6)	19 (6.0)	−2.4 (−5.8 to 0.9)
Hypoglycemia (glucose concentration <2.2 mmol/L)	35 (11.4)	34 (10.8)	0.6 (−4.4 to 5.5)
Intraventricular hemorrhage grade I or II	0 (0)	1 (0.3)	−0.3 (−0.9 to 0.3)
Subdural or intracerebral hematoma	0 (0)	1 (0.3)	−0.3 (−0.9 to 0.3)
Composite neonatal morbidity			
Intraventricular hemorrhage	0 (0)	1 (0.3)	−0.3 (−0.9 to 0.3)
Periventricular malacia	0 (0)	0 (0)	NA
Proven sepsis	0 (0)	1 (0.3)	−0.3 (−0.9 to 0.3)
Nectrotizing enterocolitis	0 (0)	0 (0)	NA
Respiratory distress syndrome	0 (0)	0 (0)	NA
Bronchopulmonary dysplasia	0 (0)	0 (0)	NA

Data were analyzed with the Student *t* test χ^2 test or Fisher exact test.
CI, confidence interval; *CNM,* composite neonatal morbidity; *MAIN,* Morbidity Assessment Index for Newborns; *NA,* not applicable.
[a] $P < .05$; [b] More than 2 consecutive readings.
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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 in which the effect of gestational age is estimated with a smoothed curve.[22] We tested for differences between the 2 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. There were no differences between the randomized groups in maternal comorbidities such as preeclampsia 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 birthweight differed significantly between the 2 groups. More babies were admitted to the 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 the 10th centile or the estimated fetal weight below the 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.

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 greater than 220 mmol/L or the need for phototherapy after induction of labor (Table 2). In Table 2, composite neonatal morbidity (CNM) is shown. When we stratified for different admission types (NICU, intermediate level care, ward), we also found comparable MAIN scores (Table 3). Stratification for different weight per-

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

Admission category	Induction of labor	Expectant monitoring	Difference in mean (95% CI)
Intensive care	n = 9 118, 136 (0–151)	n = 10 363, 203 (101–650)	n = 19 –244 (–520 to 31)
Intermediate care	n = 143 88, 0 (0–151)	n = 111 104, 98 (0–151)	n = 254 −19.26 (−49 to 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 to 12)
Growth centiles			
Less than p 2.3	n = 38 90, 0 (0–151)	n = 93 85, 0 (0–151)	n = 131 5 (−45 to 55)
p 2.3-p 5	n = 79 50, 0 (0–103)	n = 74 39, 0 (0–0)	n = 153 11 (−18 to 40)
p 5-p 10	n = 83 50, 0 (0–0)	n = 60 39, 0 (0–0)	n = 143 11 (−28 to 52)
p 10-p 75	n = 107 23, 0 (0–0)	n = 86 34, 0 (0–0)	n = 193 −11 (−43 to 25)
Greater than p75	n = 10, 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.
CI, confidence interval; *NA*, not applicable.

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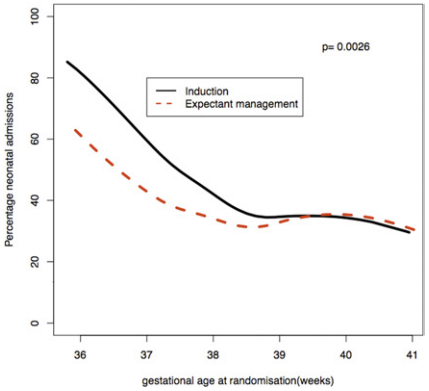
centiles showed no differences between the MAIN score (Table 3). Five children were admitted to intensive care with a MAIN score of zero.

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.

FIGURE 2
Gestational age at randomization vs percentage of neonatal admission



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We also compared the percentage of babies born after induction of labor with a positive MAIN score with babies born after an expectant management. Although we found fewer babies with a positive MAIN score beyond 38 weeks' randomization as compared with randomization at 36 or 37 weeks, the percentages in the 2 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 the 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 3 outcomes (neonatal admissions, positive MAIN score, and composite adverse outcome), we compared induction vs expectant management in women randomized before 38 weeks, from 38 to 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, 6.7–26%; $P = .001$).

COMMENT

This study confirmed findings of the DIGITAT, in which 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 birthweight, rather than because of defined complications.

Our study was limited to babies suspected of growth restriction at term,

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

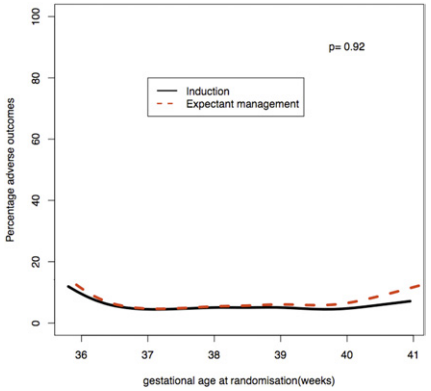

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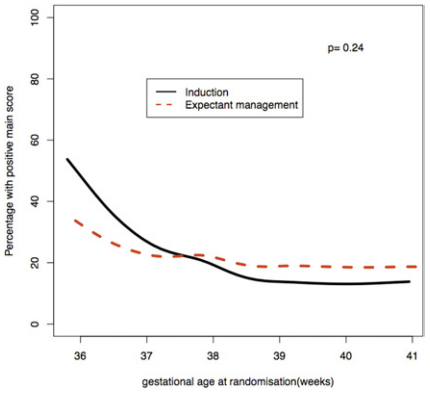
FIGURE 4
Gestational age at randomization vs percentage of neonates with a positive MAIN score



MAIN, Morbidity Assessment Index for Newborns.

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which is when most IUGR is detected.[23] In the DIGITAT, approximately 70% of children in fact had a birthweight below the 10th centile, with a higher percentage of very low birthweight (less than P2.3) after expectant management. Apparently the group of patients with suspected growth restriction is mixed, with some babies who are really growth restricted in which normal physiological growth is inhibited and others who are small for gestational age but grow along their own growth trajectory. The 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[21] (235). The neonates in our study showed no or minimal morbidity, whereas the score of Verma et al indicated mild morbidity for neonates with an IUGR. One explanation is that we limited our study to pregnancies beyond 36 weeks, whereas Verma et al included neonates from 28 weeks onward. Another explanation might be that we used discharge summaries, whereas Verma et al used full hospital records to calculate the MAIN score. Finally, the growth restriction in our population was less severe than the patients included in the study of Verma et al, which defined IUGR as a birthweight below the third centile.

The fact that 5 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 birthweight rather than morbidity. Even though admission to the NICU implies serious morbidity, these children were admitted mainly for neonatal observation. For example, 1 child in the expectant management group was admitted to the NICU with a birthweight of 1670 g but no serious morbidity.

During the trial, the IUGR pregnancies were closely monitored, and therefore, we cannot 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 in which such monitoring cannot be provided. This monitoring also might explain why our morbidity as defined by the 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 birthweight above the 10th percentile, which reminds us of the challenges of defining true growth restriction prenatally.

Children born with a low birthweight 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 birthweight, compared with longer exposure to an undernourished intrauterine environment, on neurocognitive 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, whereas 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 birthweight below the third percentile,[6,17] and we found a higher percentage of these very low birthweights after expectant monitoring.[18]Therefore, in the presence of other pathological 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 preempt 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, whereas strictly monitoring the mother and child may prevent complications of late prematurity. Late effects of these policies need further study. ■

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