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Which intrauterine growth restricted fetuses at term benefit from early labour induction? A secondary analysis of the DIGITAT randomised trial

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ABSTRACT

Objective: The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT trial) showed that in women with suspected intrauterine growth restriction (IUGR) at term, there were no substantial outcome differences between induction of labour and expectant monitoring. The objective of the present analysis is to evaluate whether maternal or fetal markers could identify IUGR fetuses who would benefit from early labour induction.

Study design: The DIGITAT trial was a multicenter, parallel and open-label randomised controlled trial in women who had a singleton pregnancy beyond 36 + 0 weeks' gestation with suspected IUGR ($n = 650$). Women had been randomly allocated to either labour induction or expectant monitoring. The primary outcome was a composite measure of adverse neonatal outcome, defined as neonatal death before hospital discharge, Apgar score <7, umbilical artery pH <7.05, or admission to neonatal intensive care. Using logistic regression modelling, we investigated associations between outcome and 17 markers, maternal characteristics and fetal sonographic and Doppler velocimetry measurements, all collected at study entry.

Results: 17 (5.3%) infants in the induction group had an adverse neonatal outcome compared to 20 (6.1%) in the expectant monitoring group. The only potentially informative marker for inducing labour was maternal pre-pregnancy body mass index (BMI). Otherwise, we observed at best weak associations between a benefit from labour induction and maternal age, ethnicity, smoking, parity, pregnancy-

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induced hypertension or preeclampsia, Bishop score and gestational age, or fetal sonographic markers (gender, estimated fetal weight, body measurements, oligohydramnios, or umbilical artery pulsatility index and end diastolic flow).

Conclusion: In late preterm and term pregnancies complicated by suspected intrauterine growth restriction, most of the known prognostic markers seem unlikely to be helpful in identifying women who could benefit from labour induction, except for maternal pre-pregnancy BMI.

1. Introduction

Intrauterine growth restriction (IUGR) refers to a condition where the fetus has failed to achieve its intrinsic growth potential due to anatomical and/or functional disorders and diseases in the feto–placental–maternal unit. IUGR affects 5–10% of pregnancies and is associated with an increased risk of perinatal mortality and morbidity, neurodevelopmental deficits during childhood and a range of diseases in adult life.

A management option for term IUGR fetuses is delivery, to release the fetus from the potentially inadequate environment. Expectant monitoring with maternal and fetal monitoring is the alternative commonly followed strategy. The Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT trial) compared labour induction with expectant monitoring in women who had a singleton pregnancy beyond 36 + 0 weeks with suspected IUGR [1,2]. The trial included 650 women and demonstrated that there are no substantial differences in outcome between induction of labour and expectant monitoring; 5.3% of fetuses in the labour induction group had an adverse neonatal outcome versus 6.1% in the expectant monitoring group. Caesarean section and instrumental vaginal delivery rates were also comparable in the treatment groups.

In practice, obstetricians are often willing to induce labour in term IUGR pregnancies for fear of still-birth, especially in the presence of maternal risk factors, abnormal fetal sonographic measurements or abnormalities of fetal Doppler velocimetry [3]. At present, there is no evidence from randomised trials on whether selecting patients for labour induction based on maternal or fetal risk factors improves perinatal and maternal outcomes. We undertook a post hoc exploratory analysis of the DIGITAT trial data, to evaluate which maternal or fetal characteristics are more likely to be helpful in identifying patients who could benefit from labour induction, compared to expectant monitoring.

2. Materials and methods

2.1. Study design and patients

The background of the trial, methods, and baseline characteristics of the randomised women has been previously reported elsewhere [2,4]. In brief, the trial included 650 pregnant women between 36 + 0 and 41 + 0 weeks' gestation, who had a singleton fetus in a cephalic presentation, suspected IUGR, and were under specialised obstetric care with no contraindication to vaginal delivery. Suspected IUGR was defined as fetal abdominal circumference below the 10th percentile, estimated fetal weight below the 10th percentile, flattening of the growth curve in the third trimester (as judged by a clinician), or the presence of a combination of any of these three factors [5].

Eligible and consenting women were randomly allocated to either labour induction (n = 321) or expectant monitoring (n = 329) (Fig. 1). In the induction group, labour was induced within 48 h after randomisation. In the expectant monitoring group, women were monitored until the onset of spontaneous delivery or delivery indications, such as suboptimal fetal heart rate tracings, prolonged rupture of membranes, postmaturity, or occurrence of severe preeclampsia.

The primary outcome was a composite measure of adverse neonatal outcome, combining the occurrence of neonatal death before hospital discharge, five-minute Apgar score of less than 7, umbilical artery pH of less than 7.05, or admission to neonatal intensive care. For each participating woman, 50 maternal and fetal characteristics were measured and recorded before randomisation at baseline. Based on a review of the literature and expert opinion, we selected 17 markers which were reportedly prognostic and therefore could have potentially been informative for treatment selection. For maternal markers we selected age, pre-pregnancy body mass index (BMI), Caucasian ethnicity, smoking, parity, presence of pregnancy-induced hypertension or pre-eclampsia in the current pregnancy, gestational age and Bishop score at randomisation. For fetal markers we evaluated gender, estimated weight (in percentiles, corrected for gestational age), oligohydramnios, biparietal distance, head circumference, abdominal circumference, femur length and umbilical artery pulsatility index and end diastolic flow. Fetal weight was estimated by the Hadlock formula [6] and the percentiles were determined using the Kloosterman's growth charts [7].

2.2. Data analysis

For each marker we developed a logistic regression model to predict the composite adverse neonatal outcome by marker, treatment, and marker-by-treatment interaction. The latter term expresses to what extent the treatment effect is associated with the marker value. In this context, we define that markers could be potentially useful for treatment selection if they show a biologically plausible qualitative interaction with treatment [8]. A marker has a qualitative interaction with treatment if it is risk factor (odds ratio >1) in one arm of trial and protective factor in the other arm of trial (odds ratio <1). The presence of a qualitative interaction would imply that for a subgroup of fetuses labour induction is

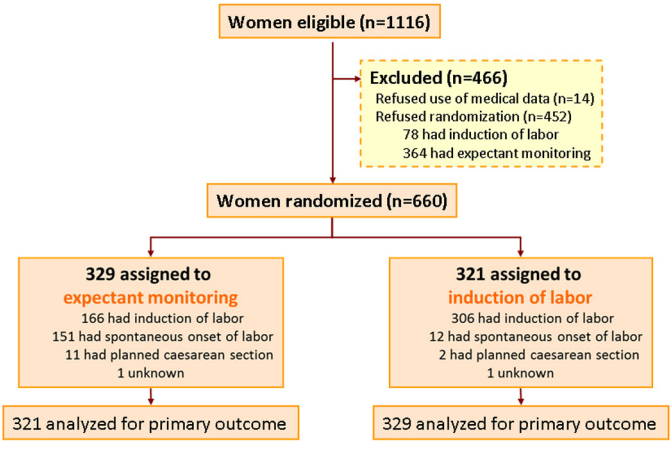

Fig. 1. Trial profile.

Table 1
Maternal and fetal characteristics of the participants in DIGITAT trial at study entry.

Baseline characteristics	Expectant monitoring (n = 329)	% missing	Labour induction (n = 321)	% missing
Maternal demographic and clinical characteristics				
Age (years)[a]	27 (23–31)	0	27 (23–31)	0
Body mass index (kg/m^2)[a]	22 (20–26)	10	22 (20–26)	14
Non-smoker (%)	48.3	9	48.3	11
Caucasian ethnicity (%)	76.9	5	76.9	5
Nulliparity (%)	61.1	0	61.1	0
Pregnancy-induced hypertension (%)	5.8	0	5.8	0
Pre-eclampsia (%)	8.2	0	8.2	0
Bishop score[a]	2 (1–4)	8	2 (1–4)	7
Foetal conditions				
Male foetus (%)	37.1	0	38.3	0
Gestational age (days)[a]	37.6 (36.8–38.5)	0	37.6 (36.8–38.5)	0
Estimated weight percentile (%)		15		21
<3rd percentile	15.0		12.4	
3–5th percentile	21.6		22.9	
5–10th percentile	36.9		35.0	
>10th percentile	26.1		29.7	
Oligohydramnios (%)	34.8	9	31.1	13
Biparietal distance percentile[a]	27 (20–41)	24	27 (20–41)	24
Head circumference percentile[a]	30 (21–41)	12	30 (21–41)	17
Abdominal circumference percentile[a]	9 (5–13)	5	9 (5–13)	6
Femur length percentile[a]	14 (7–22)	7	14 (7–22)	7
Pulsatility index of the umbilical artery[a]	0.9 (0.8–1.1)	16	0.9 (0.8–1.1)	18
Absent umbilical artery end diastolic flow	2.7	20	2.5	13.7

[a] Median (interquartile range).

beneficial, and for the other subgroup expectant monitoring is beneficial. Given the exploratory nature of our analysis, we focus on the magnitude of the interaction and the associated precision, not on statistical hypothesis testing. All analyses were done using R for Windows (Version 2.11.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Baseline characteristics of the women and fetuses who participated in the DIGITAT trial are summarised in Table 1. Induction group infants were born 10 days earlier (95% CI: 9–11 days) and weighed 130 g less (95% CI: 77–188 g) than babies in

Table 2
The relationship between maternal characteristics and the occurrence of adverse neonatal outcome is shown separately in women who underwent expectant monitoring and in whom the labour was induced. For each biomarker, odds ratios (OR) show the relative change in the risk per unit increase in the marker. The interaction OR presents the ratio of the two odds ratios.

Maternal characteristics	Expectant monitoring			Labour induction			Interaction OR
	Subgroup size	Adverse neonatal outcome (%)	Odds ratio (95% CI)	Subgroup size	Adverse neonatal outcome (%)	Odds ratio (95% CI)	
Age (years)[a]			0.95 (0.9–1.0)			0.94 (0.8–1.0)	1.01 (0.89–1.16)
15–25	118	9.3 (5–16)		113	8.0 (4–15)		
25–30	101	3.0 (1–9)		113	4.4 (2–10)		
30–42	110	5.4 (2–12)		95	3.2 (1–10)		
Body mass index (kg/m^2)[a]			1.06 (1.0–1.1)[c]			0.97 (0.9–1.1)[c]	1.09 (0.96–1.24)
15–20	80	2.5 (0–10)		79	7.6 (3–16)		
20–25	133	5.3 (2–11)		122	6.7 (3–13)		
25–33	82	11.0 (5–20)		74	4.0 (1–12)		
Ethnicity			1.15 (0.4–2.5)[c]			0.68 (0.2–2.5)[c]	1.69 (0.25–11.11)
Caucasian[b]	253	5.9 (3–10)		254	5.9 (3–10)		
Non-Caucasian	59	6.8 (2–17)		50	4.0 (1–15)		
Smoker			0.75 (0.3–1.9)			0.88 (0.3–2.3)	0.86 (0.23–3.27)
Yes	170	5.0 (2–10)		180	5.0 (2–10)		
No[b]	159	6.9 (4–12)		141	5.7 (3–11)		
Parity			0.65 (0.2–2.0)			0.31 (0.1–1.4)	2.08 (0.32–13.48)
Nulliparous	128	4.5 (2–11)		125	3.4 (1–9)		
Multiparous[b]	201	8.5 (5–14)		196	8.1 (5–14)		
Pregnancy-induced HTN or Pre-eclampsia			2.31 (0.3–19.6)			1.06 (0.1–8.4)	1.99 (0.17–23.01)
Present	46	10.9 (4–24)		27	7.4 (1–26)		
Absent[b]	283	5.3 (3–9)		294	5.1 (3–8)		
Bishop score[a]			0.96 (0.8–1.2)			0.93 (0.7–1.2)	1.04 (0.72–1.48)
0–2	51	7.8 (3–20)		48	2.1 (0–12)		
2–4	113	5.3 (2–12)		117	6.0 (3–12)		
4–10	93	7.5 (3–15)		109	4.6 (2–11)		

[a] The odds ratios are calculated using the variables as a continuous factor and not a categorical factor. The categories presented here are just made for presentation purposes.
[b] Reference category.
[c] The interaction is qualitative; indicating that for example if the marker is risk factor (odds ratio >1) for the outcome under the strategy of expectant monitoring, it is protective factor (odds ratio <1) under the labour induction strategy, or vice versa.

the expectant monitoring group. No fetal or neonatal death occurred in the study. In the labour induction group 20 infants (6.1%) had an adverse neonatal outcome compared to 17 (5.3%) in the expectant monitoring group, which indicated that induction of labour and expectant monitoring are comparable in their risk of adverse neonatal outcome (−0.8% risk difference; 95% CI: −4.3–3.2%).

Table 2 summarizes the results of our analysis of the associations between maternal markers and treatment outcome. In the expectant monitoring group, fetuses of younger mothers were at a slightly higher risk of adverse neonatal outcome; the older the mother, the lower the risk (odds ratio (OR) 0.95), but this association was also present in women in whom labour was induced (OR 0.94). These findings do not suggest that maternal age could be informative for the choice of labour induction.

In contrast, the pre-pregnancy maternal BMI could potentially be informative for the choice of treatment. In the expectant monitoring group, a higher pre-pregnancy BMI was associated with a higher risk of adverse neonatal outcome (OR 1.06), while in the labour induction group the higher BMI was associated with a lower risk (OR 0.97). This implies that fetuses of mothers with high pre-pregnancy BMI might benefit from labour induction, while fetuses of normal and low BMI mothers might be better off with expectant monitoring. Fetuses of non-caucasian mothers were at higher risk of adverse neonatal outcome when monitored expectantly (OR 1.15), but the risk was reduced in the labour induction group (OR 0.68). Ethnicity might therefore also be a potential marker for the choice of treatment. We found no other qualitatively differential marker-treatment association, suggesting that it is unlikely that maternal smoking status, parity, hypertensive disorders of pregnancy, Bishop score and gestational age could have any potential for treatment selection.

Table 3 presents the 10 investigated fetal markers and their association with the risk of adverse neonatal outcome in the two management strategies. Male fetus, lower estimated fetal weight, presence of oligohydramnios and elevated umbilical artery pulsatility index were factors generally associated with a mild increase in the risk of adverse neonatal event, but we did not observe that induction of labour could reduce the increased risk of these fetuses. Absence of umbilical artery end diastolic flow was seen in only 2.6% of fetuses and due to the very small size of the subgroup we have limited precision in evaluating a differential association with treatment outcome, and to assess if this could be helpful for treatment selection. None of the studied fetal body

Table 3
The relationship between fetal characteristics and the occurrence of adverse neonatal outcome is shown separately in women who underwent expectant monitoring and in whom the labour was induced. For each biomarker, odds ratios (OR) show the relative change in the risk per unit increase in the marker. The interaction OR presents the ratio of the two odds ratios.

Fetal characteristics	Expectant monitoring			Labour induction			Interaction OR
	Subgroup size	Adverse neonatal outcome (%)	Odds ratio (95% CI)	Subgroup size	Adverse neonatal outcome (%)	Odds ratio (95% CI)	
Gender			1.40 (0.6–3.5)			1.87 (0.7–5.0)	0.74 (0.20–2.85)
Male	107	8.4 (4–16)		105	8.6 (4–16)		
Female[b]	180	6.1 (3–11)		174	4.6 (2–9)		
Gestational age[a]			0.97 (0.7–1.3)			0.91 (0.6–1.4)	1.06 (0.61–1.86)
36 wk	80	8.7 (4–18)		77	6.5 (2–15)		
37 wk	102	5.9 (2–13)		99	6.1 (2–13)		
≥ 38 wk	101	6.9 (3–14)		103	5.8 (2–13)		
Estimated foetal weight[a]			1.52 (0.6–3.9)			2.00 (0.6–6.5)	0.76 (0.45–4.2)
<3rd percentile	89	9.0 (4–17)		39	10.3 (3–25)		
3–5th percentile	69	5.8 (2–15)		72	5.7 (2–14)		
5–10th percentile	52	5.8 (2–17)		75	6.7 (2–16)		
≥10th percentile	76	6.6 (2–15)		93	4.3 (1–11)		
Oligohydramnios			1.58 (0.6–4.1)			1.31 (0.5–3.5)	1.21 (0.41–5.9)
Present	101	8.3 (4–15)		87	7.9 (3–16)		
Absent[b]	194	5.2 (2–10)		192	6.1 (3–11)		
Biparietal distance[a]			1.00 (0.9–1.1)			0.99 (0.9–1.1)	1.01 (0.97–1.05)
<10th percentile	14	0 (0–27)		24	8.3 (1–28)		
≥10th percentile	235	6.4 (4–11)		208	5.87 (3–10)		
Head circumference[a]			1.02 (1.0–1.1)			0.98 (0.9–1.0)	1.04 (0.98–1.09)
<10th percentile	14	0 (0–27)		11	9.1 (0–43)		
≥10th percentile	275	6.6 (4–10)		256	5.5 (3–9)		
Femur length[a]			1.01 (0.9–1.1)			0.98 (0.9–1.1)	1.03 (0.98–1.09)
<10th percentile	107	6.5 (3–13)		106	6.6 (3–14)		
≥10th percentile	195	5.6 (3–10)		192	5.2 (3–10)		
Abdominal circumference[a]			1.01 (0.9–1.1)			0.90 (0.8–1.0)	1.12 (0.99–1.27)
<10th percentile	185	4.9 (2–9)		169	7.7 (4–13)		
≥10th percentile	126	7.1 (4–14)		134	3.0 (1–8)		
Umbilical artery pulsatility index (UA-PI)[a]			1.47 (0.2–12.0)			1.08 (0.1–9.2)	1.37 (0.05–35.88)
<0.9	105	5.7 (2–13)		87	3.4 (1–10)		
0.9–1.1	101	3.8 (1–10)		89	9.0 (4–17)		
≥1.1	71	8.4 (3–18)		86	5.8 (2–14)		
Umbilical artery end diastolic flow			2.49 (0.3–1.9)[c]			0 (0–NA)[c]	NA
Present[b]	255	6.4 (4–10)		270	6.8 (4–11)		
Absent	7	16.7 (1–60)		7	0 (0–44)		
Reversed	0	–		0	–		

NA: not available.
[a] The odds ratios are calculated using the variables as a continuous factor and not a categorical factor. The categories presented here are just made for presentation purposes.
[b] Reference category.
[c] The interaction is qualitative; indicating that for example if marker A is a risk factor (OR > 1) for the outcome under the strategy of expectant monitoring, it is protective factor (OR < 1) under the labour induction strategy, or vice versa.

measurements showed any potential for identification of fetuses who could benefit from inducing labour.

4. Comments

In this study of late preterm and term growth-restricted fetuses we could investigate the potential of 17 well-known maternal and fetal risk factors of adverse neonatal outcome for identification of fetuses who could benefit from labour induction. Maternal pre-pregnancy BMI was the most promising factor, leading to the hypothesis that, in late-preterm IUGR, labour induction might be beneficial in women with a high pre-pregnancy BMI. Our analysis also suggested that in women of non-caucasian ethnicity labour induction might be beneficial, but the small size of this subgroup and the relatively rare outcome do not allow us to make firm statements.

Overall, the lack of precision is more of a problem with binary risk factors that are not very common, like umbilical artery end diastolic flow. We are aware of this limitation, but considered it worthwhile to explore the association between the markers and the benefit from labour induction, for producing hypotheses for treatment selection that can be tested and validated in future studies.

Our analysis is based on a randomised trial data of 650 IUGR-suspected pregnancies, where patients had been randomly allocated to expectant monitoring strategy or immediate labour induction. There was no selection bias: none of the evaluated baseline maternal and fetal risk factors had affected the choice of treatment.

A considerable proportion of small for gestational age (SGA) fetuses are constitutionally small and not at increased risk of perinatal morbidity and mortality. In the remaining proportion of SGA fetuses, growth is pathologically restricted, mainly due to placental insufficiency. Finding markers that could identify growth-restricted fetuses would therefore be valuable, especially if earlier delivery of these fetuses reduces their expected high risk of adverse perinatal outcomes. A series of physiological markers have been proposed, such as sex or maternal age, height, body mass index, ethnicity and parity [10,11]. If an SGA fetus is female or from a non-caucasian, nulliparous mother with short height or low weight, the chances that it is constitutionally small are considered to be higher [12]. Our analysis supports this hypothesis about gender of fetus, nulliparity and maternal pre-pregnancy BMI, but only pre-pregnancy BMI seems to be potentially useful for treatment selection.

In general, there is an inverse relationship between fetal weight percentile and adverse perinatal outcomes. In a recent study by Pilliod and colleagues, the risk of intrauterine fetal death in non-anomalous fetuses under the 3rd percentile of weight was as high as 58 per 10,000 versus 5 per 10,000 in non-IUGR fetuses [13]. Although the risk is more than 10 times that of the non-IUGR fetus, the difference in the risk is as small as 0.5%. We also observed in our study participants that fetuses with an estimated weight under the 3rd percentile were at slightly higher risk of adverse neonatal outcomes compared to other IUGR fetuses, but labour induction could not reduce this risk. These fetuses are generally at a slightly higher risk, and early delivery by labour induction does not seem to change this risk.

In a systematic review and meta-analysis of six good-quality trials, Westergaard and colleagues concluded that the use of umbilical artery Doppler velocimetry in pregnancies with suspected IUGR and/or hypertensive disease of pregnancy reduces the number of perinatal deaths and unnecessary obstetrics interventions [14]. A comparison of our patient population with that of their pooled analysis shows that the systematic review included higher risk pregnancies; the perinatal death rate in the pooled analysis was about 2%, where we had no perinatal death in 650 patients. Their meta-analysis included women as early in their pregnancy as 24 weeks, which may contribute to the higher risk of perinatal mortality and also to the observed benefit of umbilical artery Doppler velocimetry. There are other proposed biomarkers such as measures of fetal brain vasodilatation that might be helpful for identifying fetuses that would benefit from interventions [15–17] but these needs to be evaluated in similar studies before they can be applied in clinical practice.

At present there is no single test that dictates the optimal timing of delivery of the growth restricted fetus. In practice, term pregnancies are often delivered and the delivery of the late preterm (34 + 0–36 + 6 weeks) or early term (37 weeks) growth-restricted fetus is also recommended if there are additional risk factors for adverse outcome, such as maternal medical/obstetrical disorders, arrest of growth over a three- to four-week interval, and/or absence or reversal Doppler flow in the umbilical artery [9]. This strategy is based on the consensus that the growth-restricted fetus should be born if the empirically estimated risk of fetal death exceeds the risk of neonatal death. The DIGITAT trial shows that the risk of neonatal morbidity and mortality in suspected growth-restricted fetuses of 36 weeks and later is rather small, provided there is adequate fetal monitoring. Except for maternal pre-pregnancy body mass index, none of the markers evaluated here seems to be informative about the benefit of labour induction in this population and setting.

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