

## **TRUFFLE Study of severe fetal growth restriction at 26-32 weeks:**

### **Key messages**

Authorship: TRUFFLE 1 investigators as per Lancet (minus those that have left the group-Calvert, Schneider) on behalf of the TRUFFLE group: this group to include TRUFFLE 1 and TRUFFLE 2 investigators that have contributed to the authorship of this document and DMEC (separately listed)

### What was the TRUFFLE study?

TRUFFLE was a prospective, European multicentre, unblinded, randomised trial that ran between Jan 1, 2005 and Oct 1, 2010 in 20 European centres. It studied singleton fetuses at 26–32 weeks of gestation who had very preterm fetal growth restriction (FGR): abdominal circumference (AC) <10th percentile **and** high umbilical artery Doppler pulsatility index (PI) [>95th percentile]. In order to assess whether changes in the fetal ductus venosus (DV) Doppler waveform or short-term variation (STV) on cardiotocography should be used as a trigger for delivery in these pregnancies, we randomly allocated the 542 included women to one of three “timing of delivery” plans (randomisation was 1:1:1).

### What were the intervention arms?

Women were randomised to three groups, so delivery was based on:

1. CTG STV - an abnormal CTG , defined as a fetal heart rate STV < 3.5 msec between 26<sup>+0</sup> to <29<sup>+0</sup> weeks of gestation and STV <4 msec between 29<sup>+0</sup> to <32<sup>+0</sup> weeks gestation; in this group the DV was not measured
2. Early DV changes (pulsatility index >95th percentile), OR CTG STV below a ‘safety net’ level (see box).
3. Late DV changes (A wave [the deflection within the venous waveform signifying atrial contraction] at or below baseline). OR CTG STV below the same ‘safety net’ (see box).

### What was the ‘safety net’?

The safety net reflected fetal monitoring parameters, agreed by consensus amongst TRUFFLE investigators, that mandated delivery irrespective of randomised group. This safety net has been applied to all patients hence if the results of this trial are implemented in guidelines or local protocols the safety net criteria must be an integral part of it. These criteria described below are taken directly from the 2004 protocol:

#### **Box: Safety net criteria for triggering delivery even when women are randomised to DV groups**

##### **STV criteria:**

*The cut off ‘rescue’ value of STV for delivering based on CTG at 26<sup>+0</sup> to <28<sup>+6</sup> weeks is if STV < 2.6 msec; and 29<sup>+0</sup> to <31<sup>+6</sup> weeks if STV < 3 msec. Or if, irrespective of STV, there are spontaneous repeated persistent unprovoked decelerations on CTG.*

##### **Umbilical artery Doppler criteria:**

*Absolute indications for delivery in all randomised arms:*

*≥32<sup>+0</sup> weeks deliver if reversed umbilical artery EDF*

*≥34<sup>+0</sup> weeks deliver if absent umbilical artery EDF.*

*Delivery may be undertaken according to local policies after 30<sup>+0</sup> weeks if there is reversed umbilical artery EDF, and after 32<sup>+0</sup> weeks if there is absent umbilical EDF.*

### What was the primary outcome of the randomized trial?

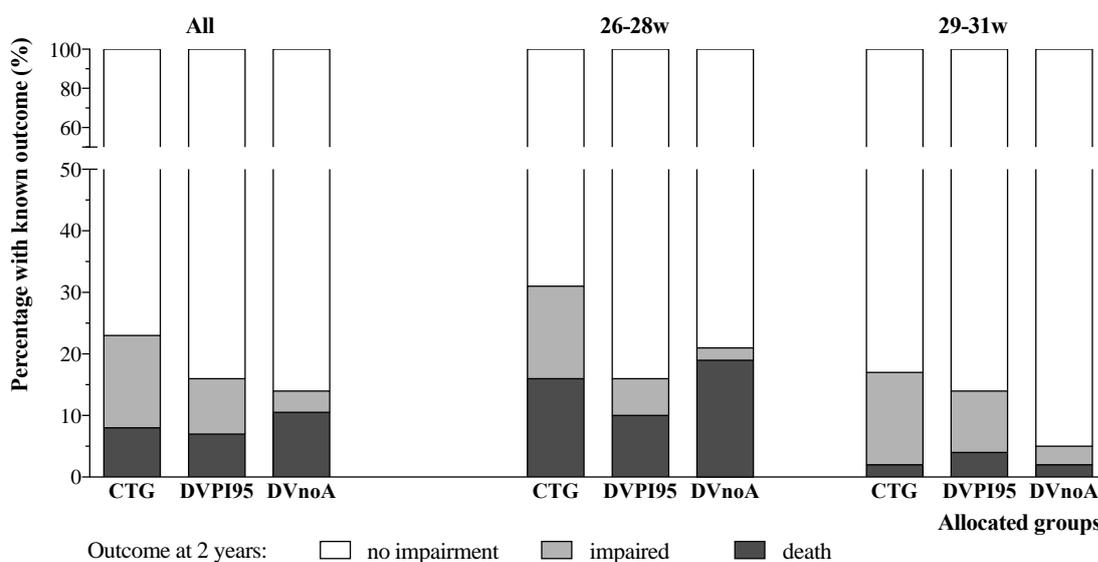
The primary outcome was survival without cerebral palsy or neurosensory impairment, or a Bayley III developmental score of less than 85, at 2 years of age.

There are two ways to look at the primary outcome. One is "survival without neurological impairment". There was no significant difference in this outcome among all pregnancies randomised, counting deaths as neurologically impaired. But neurological assessment is only possible in surviving infants, and because of this the protocol specified a primary analysis restricted to surviving infants. This is also on the grounds that it is an outcome important to parents. On this analysis there were significantly more neurologically intact babies at two years in the 'deliver on late ductus venosus changes with CTG safety net' group; the proportion without neurodevelopmental impairment at 2 years was 85% in the CTG group, 91% in the early ductus venosus group and 95% in the late ductus group. Both analyses were included in the main trial report, Lancet 2015. In clinical practice, 'deliver on late ductus venosus changes with CTG safety net' is therefore the policy which the TRUFFLE group recommends.

### What were the key findings of the TRUFFLE study overall?

In severe early onset fetal growth restriction, the median gestational age at delivery was 30.7 weeks (IQR 29.1–32.1) and mean birthweight was 1019 g (SD 322). Over 80% of babies survived and had no demonstrable neuro impairment at 2 years of age; 12 fetuses (2%) died in utero despite close monitoring; and 27 (6%) neonatal deaths occurred. The cerebral palsy rate was around 1%, in other words much lower than frequently quoted. Nearly three quarters of women developed gestational hypertension: in this case the pregnancies proceeded for a median of just under one week. If no hypertension developed, the median time from diagnosis to delivery was two weeks.

The bar chart shows the proportion of babies overall with no impairment, impairment or death recruited at 26-28 weeks and 29-31 weeks.



**Did the TRUFFLE babies reflect a highly selected sample?**

Early onset fetal growth restriction is not common, so in that sense yes. But after excluding those fetuses affected by congenital abnormalities, chromosomal conditions and infections (based on a careful ultrasound scan, chromosomal testing where indicated and a blood infection screen), most had growth restriction due to utero-placental insufficiency. These investigations are all routinely carried out in European fetal medicine settings and are applicable to any such setting.

**Are the TRUFFLE results generalizable?**

They are generalizable to settings where high level neonatal facilities exist, where there is specialist fetal medicine expertise and the ability to undertake arterial and venous Doppler assessments regularly and where computerised CTG (cCTG) is available.

**Why was the prevalence of adverse outcomes in TRUFFLE lower than anticipated?**

The better than expected outcomes probably reflected the benefit of being in a trial and being closely looked after by expert obstetric teams, and also expert neonatal care. We would like to suggest that this is a good reason for women to join trials in obstetrics; that patients with a specific condition should be entered into a study early; and that clinical care in early onset growth restriction should be undertaken in tertiary level units or other centres of excellence.

**Neurological outcome at 2 years of age was better in the late DV group. This means that I can manage these pregnancies with Doppler and without cCTG?**

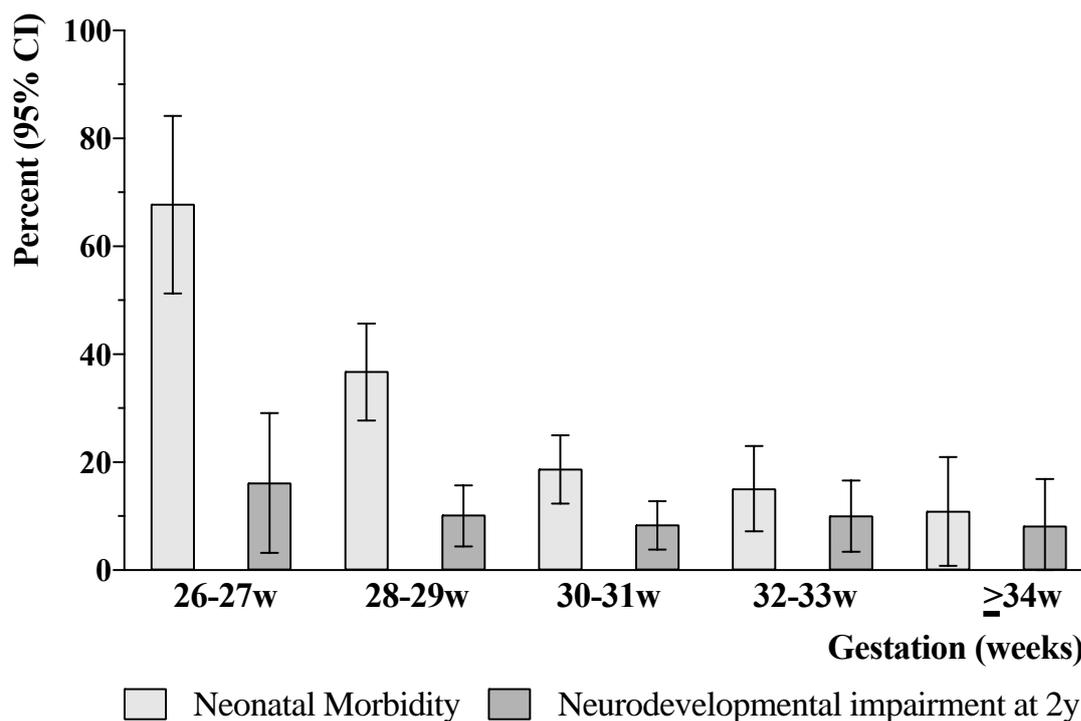
No. Monitoring has to consist of a package, which includes cCTG at 'safety net' level alongside DV Doppler. In this context it should not be forgotten that in the DV groups twice as many fetuses were delivered on the basis of CTG safety net criteria than on DV changes. Moreover the somewhat poorer outcome in the cCTG group might be explained by absence of a DV safety net in that group, whereas the DV groups had a cCTG safety net. You can expect outcomes similar to those of the TRUFFLE study only by using DV Doppler and cCTG in association.

**My hospital doesn't use cCTG, can I use normal CTG?**

We don't recommend this. The CTG monitoring in the TRUFFLE study was based on computerized assessment of fetal heart short term variation (STV). This is the only objective measure of fetal heart rate that has been validated against invasive testing in fetal hypoxia and acidaemia. Simple visual interpretation of a regular CTG is not sufficiently informative, nor objective enough to provide reassurance about fetal condition. The cCTG equipment used calculated short term variation (STV) based on the Dawes-Redman algorithm. Should fetal heart rate decelerations occur, these may however be assessed visually without recourse to computerized CTG.

### Did neurodevelopmental impairment (NDI) change with gestational age and was it related to neonatal morbidity (NNM)?

An important strength of TRUFFLE is that babies were followed up to the age of 2 years, allowing assessment of NDI. The overall rate of NDI was 10%. Although NNM was a risk factor for NDI, in most infants with NDI this was not preceded by NNM. NDI is thought to result from brain damage, related to fetal growth restriction, regardless of gestational age.



Bar chart describing rates within gestational age groups of severe neonatal morbidity (NNM, a composite of one or more of the following severe morbidities: bronchopulmonary dysplasia, severe germinal matrix cerebral haemorrhage grades 3 and 4, cystic periventricular leukomalacia, proven neonatal, necrotizing enterocolitis) and of neurodevelopmental impairment (NDI, a composite of one or more of the following: a cognitive Bayley III score <85, disabling cerebral palsy, hearing loss requiring hearing aids or severe visual loss) in surviving children. There were 31 children born at 26-27 weeks, 109 children born at 28-29 weeks, 145 children born at 30-31 weeks, 80 children born at 32-33 weeks and 37 children born at >33 weeks. There was a significant relation between NNM and gestational age ( $p < 0.001$ ), but not between NDI and gestational age ( $p = 0.40$ ).

### But many women in the Doppler group were delivered for reasons other than abnormal ductus venosus Doppler?

Yes—that is true: delivery was undertaken for severe pre-eclampsia or HELLP syndrome in 54 (11%) women and for fetal distress not based on the study protocol in a further 55 (11%) women. But such “off protocol” decisions are a frequent feature of randomised controlled studies. It is generally recommended to undertake an “intention to treat” analysis, in other words, what the intended

delivery criteria were rather than what the actual reason for delivery was. This is because when the decision is made to monitor an individual woman with a certain modality, it is not known what factors will intercede in future.

Of course, many women were delivered per protocol before 32 weeks, and this included by cCTG 'safety net' indication in the early and late DV groups. The paper by Visser ( ) details these outcomes: in mothers delivered according to ductus venosus changes, there was a lower rate of survival without neurodevelopmental impairment in the CTG group. In the CTG group, fetuses were monitored by heart rate monitoring and umbilical artery Doppler only. The finding that many deliver for other reasons means that CTG, which was integral part of the three arms, is a key component of the monitoring strategy and should not be disregarded.

### **Why should the neurodevelopmental outcomes be better in survivors within the ductus venosus groups?**

We don't know. Many hypotheses have been advanced however all are speculative as the TRUFFLE study could not answer this question directly.

### **Why were there more fetal deaths in the late ductus group?**

Fetal deaths were categorized as unexpected, or due to planned non-intervention. In total there were 2 fetal deaths in the CTG group, 4 in the early ductus group and 6 in the late ductus group. Assessment of the monitoring parameters that were obtained shortly before fetal death in the 7 unexpected cases of fetal death showed an abnormal CTG in only 1. Hence 6 out of 7 cases would not have been delivered in the other arms of the trial based on monitoring data. The other deaths were inevitable (parents declined intervention) or congenital abnormality (Ganzevoort 2017).

### **Do the findings of the study still hold true for babies delivered according to the randomized indication before 32 weeks?**

Yes. In the study by Ganzevoort ( ), outcomes prior to 32 weeks were significantly better in those women randomized to the ductus venosus Doppler groups compared to the CTG group.

### **Did giving corticosteroids affect Doppler and CTG measurements?**

The paper by Prefumo ( ) shows that although corticosteroids had a small effect increasing CTG STV only on the day following administration, this change was very small. There were no changes in DV or Umbilical/middle cerebral artery (UC) pulsatility index ratio. This means that an abnormal CTG a few days after administration of corticosteroids should not be disregarded because of a presumed corticosteroid effect.

### **Given the current interest in the cerebral circulation, should we deliver based on MCA PI, CPR or UC ratio?**

No. The paper by Stampalija (AmJOG 2017) shows weak associations between middle cerebral artery Doppler and short term neonatal outcome, and MCA and UC ratio with 2-year neurodevelopmental outcome. These indices are may be informative in understanding the pathophysiological process but have no proven benefit in the monitoring-management strategy. The most important determinants of outcome are gestational age at delivery and birthweight.

### **How often should we monitor severe fetal growth restriction?**

There is no international consensus on the frequency of monitoring in early FGR. In the UK, the RCOG green-top guideline “Management of small for gestational age” states:

*In SGA fetuses with abnormal umbilical artery Doppler where there is not an indication for delivery the optimal frequency of surveillance is unclear. Until definitive evidence becomes available it is **reasonable** to repeat surveillance twice weekly in fetuses with end–diastolic velocities present and daily in fetuses with absent or reversed end–diastolic velocities (AREDV). (Level 4 Evidence)*

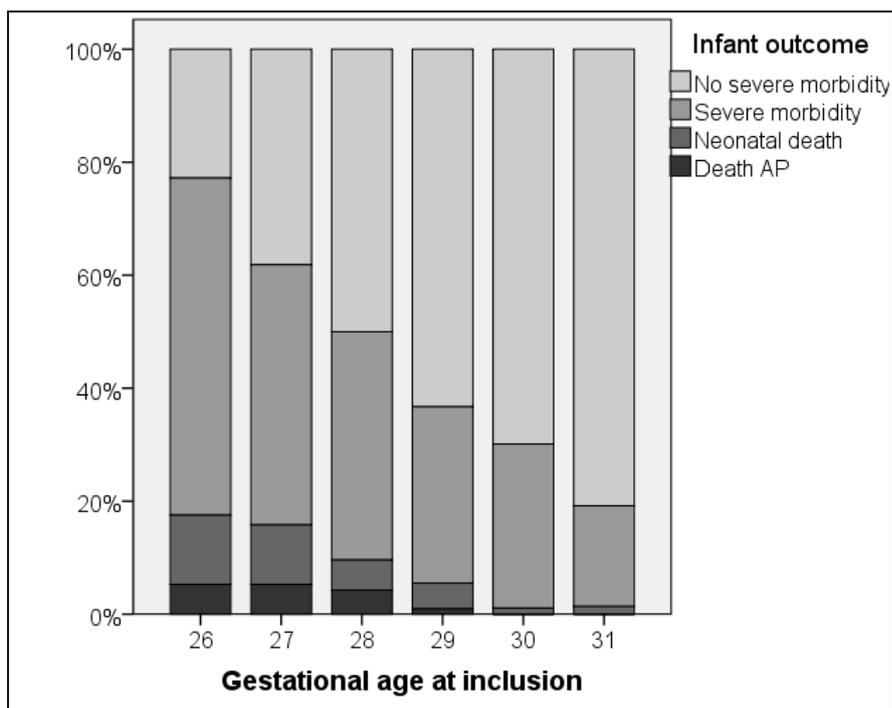
The study by Wolf ( ) suggests that unless CTG STV monitoring is undertaken daily, there is a 5% risk of missing an abnormally low STV. We do not know whether a low STV would have recovered subsequently, and the TRUFFLE study was not intended to define an ideal monitoring regimen. Based on these results daily CTG STV may be initiated but given the very low risk of intra uterine death in the TRUFFLE cohort monitoring twice weekly with CTG STV and Doppler is an appropriate minimum, agreed through consensus by TRUFFLE investigators.

### **How often should we monitor maternal blood pressure?**

We found that 70% of women where there was FGR developed gestational hypertension. The TRUFFLE study did not evaluate the optimal frequency of blood pressure monitoring. The TRUFFLE group consensus is to recommend checking blood pressure and urinary protein:creatinine ratio (or using dip-stick analysis) at each visit or at least weekly in asymptomatic women with FGR.

### **How can I use the TRUFFLE results for counselling?**

These two bar charts, taken from the TRUFFLE report of perinatal morbidity and mortality analysed as a cohort (Lees UOG 2013) may be useful in counselling. They give the main outcome data split by gestation for both counselling women at study inclusion, and then at delivery. For example, if a woman is diagnosed with FGR at 28 weeks, the bar chart ‘at inclusion’ is used.



If her pregnancy proceeds to 30 weeks and there is a plan to deliver, the chart 'at delivery' can be used to update the counselling:

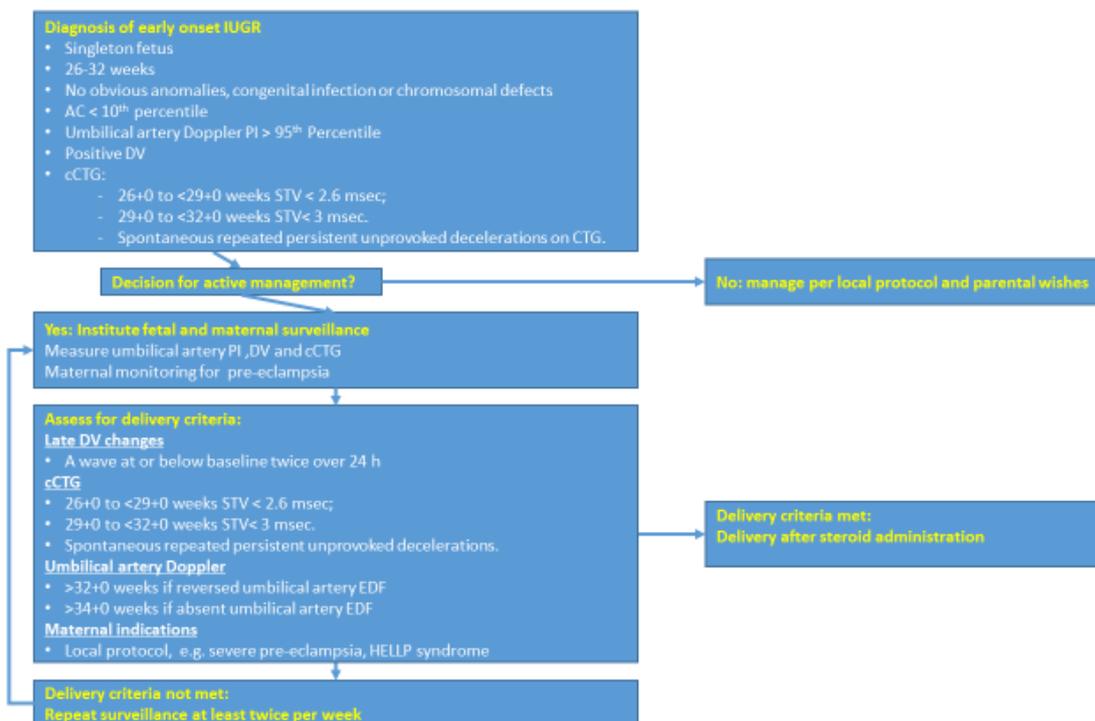


### Some pregnancies continued beyond 32 weeks, what happened to them?

They were delivered according to the local protocols. In general, this meant delivery was undertaken at 30-32 weeks if there was umbilical reversed EDF, at 32-34 weeks in absent EDF, and at beyond 34 weeks if the umbilical artery PI was raised.

As the upper gestation age at recruitment to TRUFFLE 1 was 31+6 weeks, the TRUFFLE study cannot answer the question as to how best to monitor and when to deliver these slightly later gestation babies. The TRUFFLE 2 randomised study under development will test different triggers for delivery in women with compromised and/or small babies at 32-37 weeks.

### Schematic:



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