ULTRASOUND in Obstetrics & Gynecology isuog

TRUFFLE study of severe fetal growth restriction at 26-32 weeks: Key messages

Journal:	*Ultrasound in Obstetrics and Gynecology*
Manuscript ID	UOG-2017-0597
Wiley - Manuscript type:	Narrative Review
Date Submitted by the Author:	14-Jul-2017
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Manuscript Categories:	
Keywords:	TRUFFLE, Fetal growth restriction, Doppler, ductus venosus, CTG, neurodevelopmental outcome, morbidity, perinatal, mortality

TRUFFLE study of severe fetal growth restriction at 26-32 weeks: Key messages

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What was the TRUFFLE study? The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) was a prospective multicentre, unblinded, randomized trial that ran between Jan 1, 2005 and Oct 1, 2010 in 20 European centres [1]. It studied singleton fetuses at 26–32 weeks of gestation who had very preterm fetal growth restriction (FGR), defined as 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 (CTG) 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 (randomization was 1:1:1).

What were the three timing of delivery arms? Women were randomized to one of three groups that mandated delivery based on either:

1. CTG STV: an abnormal CTG , defined as a fetal heart rate STV < 3.5 msec between 26^{+0} to 28^{+6} weeks of gestation or STV <4 msec between 29^{+0} to 31^{+6} weeks gestation; in this group the DV was not measured;
2. Early DV changes: A DV pulsatility index >95th percentile, OR CTG STV below a 'safety net' level (see box).
3. Late DV changes: The DV A-wave (the deflection within the venous waveform signifying atrial contraction) at or below the baseline. OR CTG STV below the same 'safety net' as group 2 (see box).

What was the 'safety net'? The safety net (see box) reflected fetal monitoring parameters, agreed by consensus amongst TRUFFLE investigators, that mandated delivery irrespective of randomized group. This safety net 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. In addition, delivery could be indicated in all groups based on maternal conditions (chiefly pre-eclampsia).

Box: Safety net criteria for triggering delivery regardless of randomized group

STV criteria:

The cut off 'rescue' value of STV for delivering based on CTG at 26^{+0} to $<28^{+6}$ weeks is if STV < 2.6 msec; and 29^{+0} to $<31^{+6}$ 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 randomized arms:

$\geq 32^{+0}$ weeks deliver if reversed umbilical artery EDF

$\geq 34^{+0}$ weeks deliver if absent umbilical artery EDF.

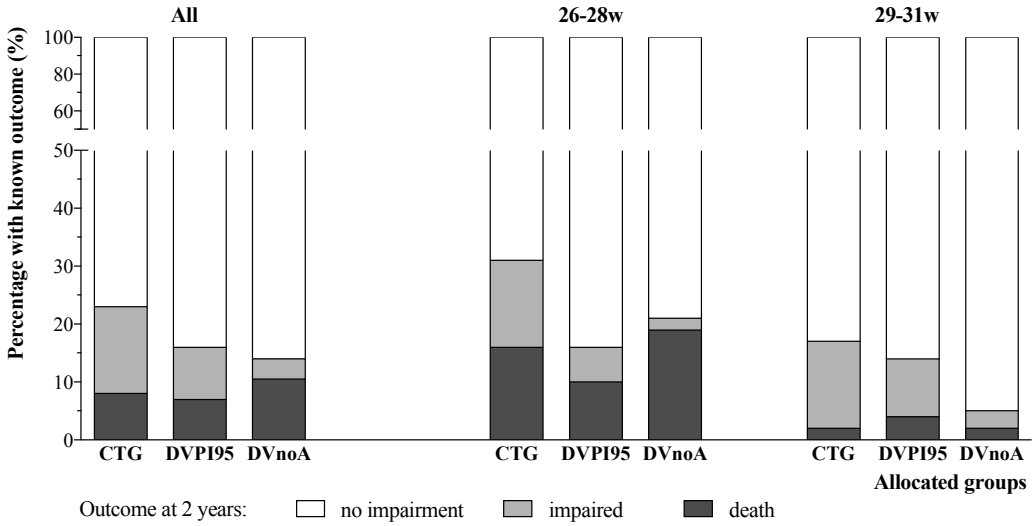
Delivery may be undertaken according to local policies after 30^{+0} weeks if there is reversed umbilical artery EDF, and after 32^{+0} weeks if there is absent umbilical EDF.

What were the results in 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 way is to assess "survival without neurological impairment" – in this composite outcome, death is in a sense equivalent to a neurologically impaired infant. There was no significant difference in this outcome among all pregnancies randomized. But as neurological assessment is only possible in surviving infants, and because of this the protocol specified a second way of analysis: one where the primary analysis is 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. This improvement in neurodevelopmental outcome was accompanied by a non-significant increase in perinatal and infant mortality. Both analyses were included in the main trial report [1]. 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 other findings of the TRUFFLE study? The median gestational age at delivery was 30.7 weeks (IQR 29.1–32.1) and mean birthweight was 1019 g (SD 322), confirming the severe early onset FGR in the women taking part. Despite this severity, outcome were better than often reported: over 80% of babies survived and had no demonstrable neurological 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%, 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 based on gestational age at recruitment: at 26-28 weeks and 29-31 weeks [2].



X- axis represents randomized groups; CTG = Delivery based on cardiotocogaphy; DVPI95 = Delivery based on DV pulsatility index >95th percentile; DVnoA = DV A-wave at or below the baseline.

Were TRUFFLE babies a highly selected sample? Early onset FGR 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. It should be noted that there is a group of even more severe early FGR - such that fetuses were not eligible for the study, for example due to not fulfilling the inclusion criteria for DV PI or STV. Consequently, the conclusions of the study should be used with caution in such fetuses.

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

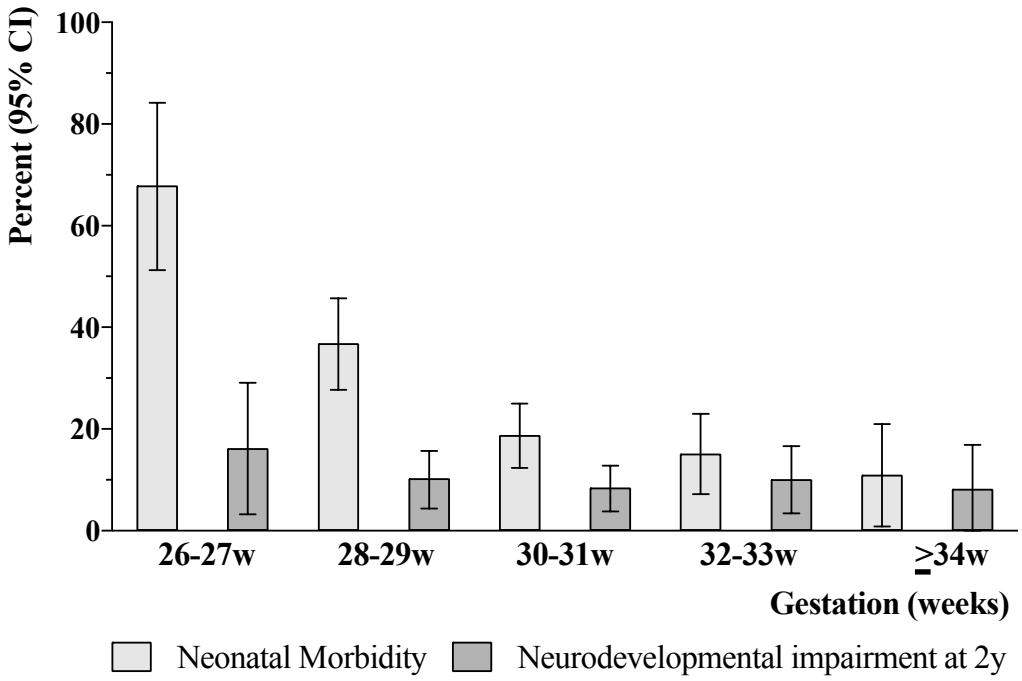
Why was the prevalence of adverse outcomes in TRUFFLE lower than anticipated? The better than expected outcomes probably reflected the benefit of being in a trial and being closely looked after by expert obstetric teams, and expert neonatal care. It suggests and that clinical care in early onset growth restriction should be undertaken in tertiary level units or other centres of excellence. In addition, it has been shown in many studies that joining trials is of benefit (even in those where an intervention proves ineffective) and this may have had a role to play [3].

Neurological outcome at 2 years of age was better in the late DV group. Does this mean I can manage these pregnancies with Doppler and without cCTG? No. The timing of delivery plan in the late DV group consisted of a package, which included 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 conjunction.

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). Although there is no randomised trial evidence against visual interpretation, cCTG 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 may not be sufficiently informative, nor objective enough to provide reassurance about the fetal condition. The cCTG equipment used calculated short term variation (STV) based on the Dawes-Redman algorithm. Computerised CTG will also detect repetitive fetal heart rate decelerations, although these may also be assessed visually. Though we have described other fetal heart rate parameters that may be better than STV for assessing fetal condition in severe growth restriction [9], these are not yet evaluated for clinical management.

Given the current interest in the cerebral circulation, should we deliver based on middle cerebral artery PI, cerebro-placental ratio or umbilical / middle cerebral artery PI ratio? No. There were weak associations between middle cerebral artery Doppler and short term neonatal outcome, and MCA and UC ratio with 2-year neurodevelopmental outcome. Although these indices may be informative in understanding the pathophysiological process, they are of no proven benefit in the monitoring or management strategy before 32 weeks of gestation [7].

Did neurodevelopmental impairment change with gestational age and was it related to neonatal morbidity? An important strength of TRUFFLE is that babies were followed up to the age of 2 years, allowing assessment of neurodevelopmental impairment (NDI). The overall rate of NDI was 10%. Although neonatal morbidity (NNM) was a risk factor for NDI, in most infants with NDI this was not preceded by NNM [10].



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 paresis, 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. This was anticipated in the trial design and does not constitute "off protocol" delivery. Such occurrences are a frequent feature of randomized 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. We have detailed these outcomes [4]: there was a lower rate of survival without neurodevelopmental impairment in those randomized to CTG (which included umbilical artery but not ductus venosus Doppler) than in mothers delivered according to ductus venosus changes. The finding that many women deliver for reasons other than DV means that CTG, which was integral part of the three arms, is a key component of the monitoring strategy and should not be disregarded.

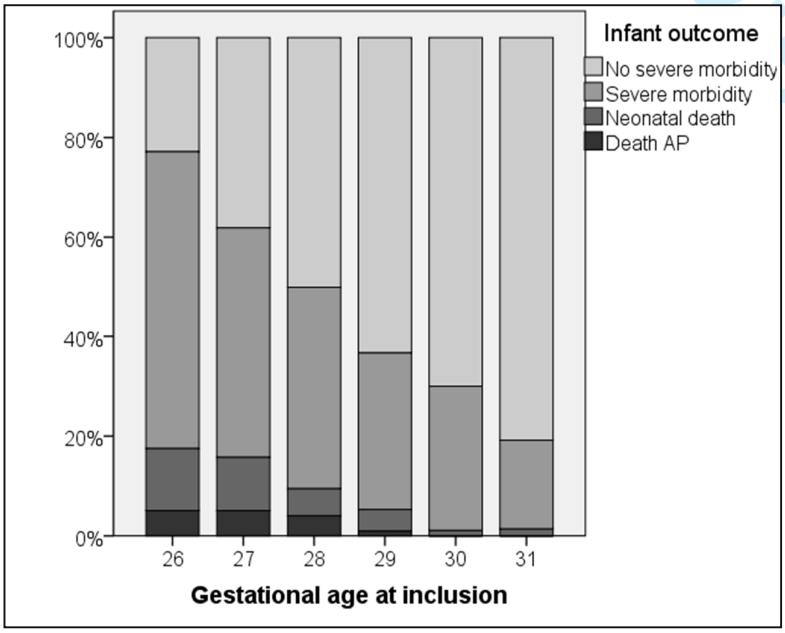
What about the fact there more fetal deaths in the late ductus group? And is there an explanation why neurodevelopmental outcomes were better in survivors within the ductus venosus groups? In

total there were 12 fetal deaths, and it is likely the differences in fetal death occurred between groups by chance. 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 due to congenital abnormality (5). The pathophysiological reason why neurodevelopmental outcomes were better in the ductus venosus groups is not elucidated by this study. However, we speculate that both CTG and ductus venosus Doppler are parameters that indicate (failing) homeostatic mechanisms. Thus, when they become abnormal, the balance of risks in intervention and expectant management slides towards intervention.

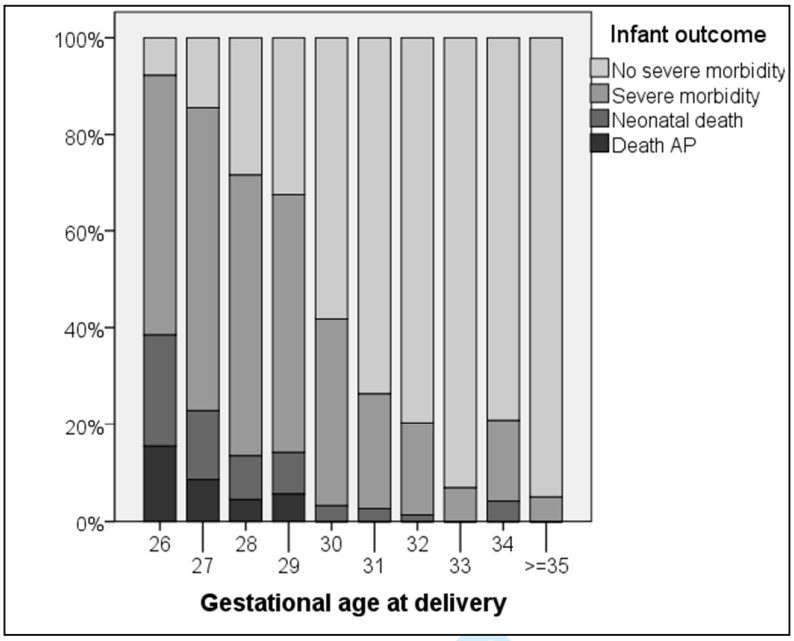
Do the findings of the study still hold true for babies delivered according to the randomized indication before 32 weeks? Yes. Outcomes prior to 32 weeks were significantly better in those women randomized to the ductus venosus Doppler groups compared to the CTG group [5].

How often should we monitor severe FGR? There is no international consensus on the frequency of monitoring in early FGR. The study by Wolf [8] 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 alternate day monitoring with CTG STV and Doppler is an appropriate minimum, as stated in the protocol agreed through consensus by TRUFFLE investigators.

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 (2) 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:



How often should we monitor maternal blood pressure? The TRUFFLE study did not evaluate the optimal frequency of blood pressure monitoring. However, we found that 70% of women where there was FGR developed gestational hypertension. Based on this it would seem reasonable 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 such severe FGR.

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 32 weeks if there was umbilical reversed EDF, at 34 weeks in absent EDF, and at beyond 34weeks if the umbilical artery PI was raised. Delivery for the same criteria at 30, 32 and beyond 32 weeks, respectively, was discretionary.

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 randomized study under development will test different triggers for delivery in women with compromised and/or small babies at 32-37 weeks.

Schematic: SEE NEW VERSION ATTACHED SEPARATELY

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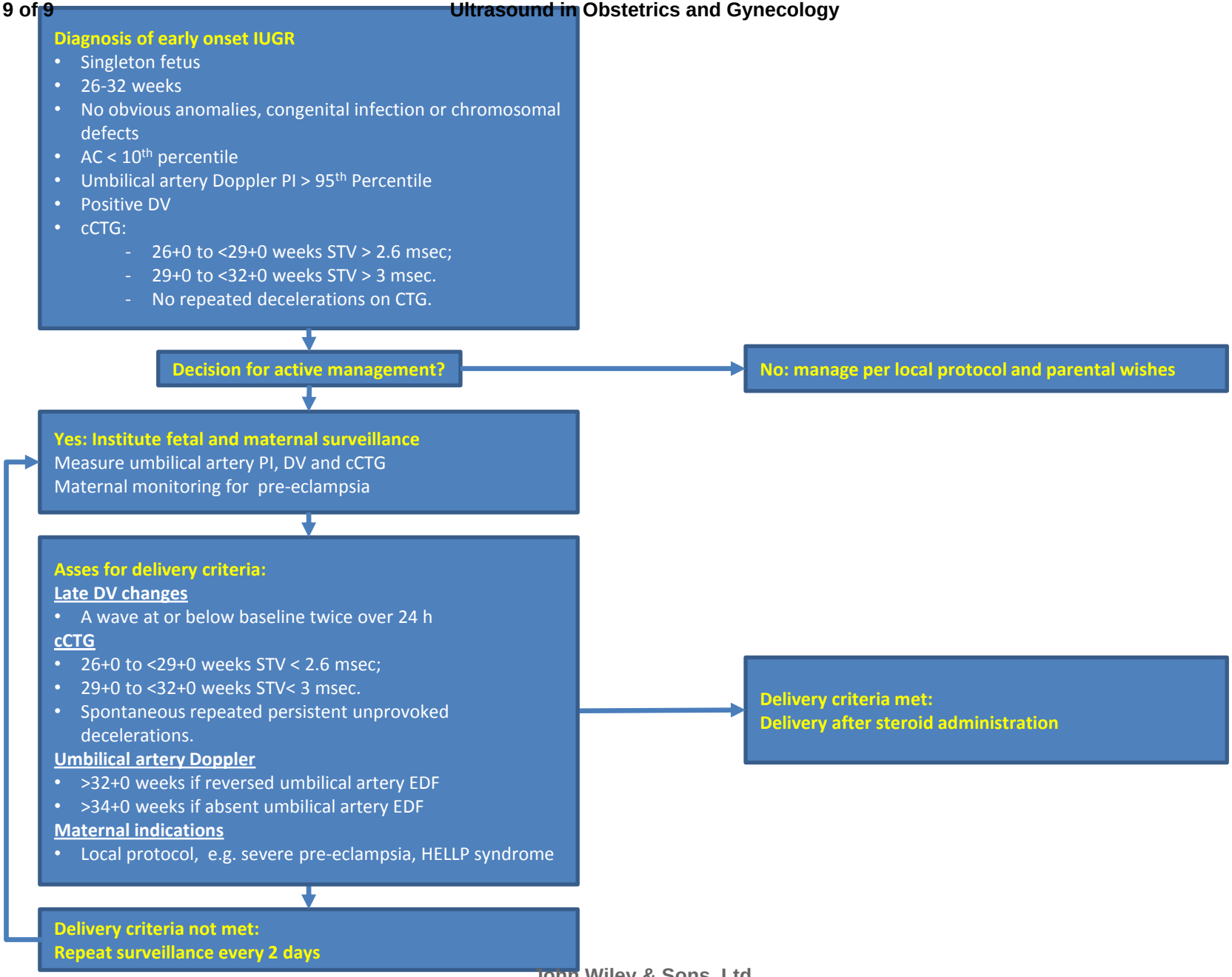
Diagnosis of early onset IUGR
• Singleton fetus
• 26-32 weeks
• No obvious anomalies, congenital infection or chromosomal defects
• AC < 10th percentile
• Umbilical artery Doppler PI > 95th Percentile
• Positive DV
• cCTG:
- 26+0 to <29+0 weeks STV > 2.6 msec;
- 29+0 to <32+0 weeks STV > 3 msec.
- No repeated decelerations on CTG.
Decision for active management?
No: manage per local protocol and parental wishes
Yes: Institute fetal and maternal surveillance
Measure umbilical artery PI, DV and cCTG
Maternal monitoring for pre-eclampsia
Asses for delivery criteria:
Late DV changes
• A wave at or below baseline twice over 24 h
cCTG
• 26+0 to <29+0 weeks STV < 2.6 msec;
• 29+0 to <32+0 weeks STV< 3 msec.
• Spontaneous repeated persistent unprovoked decelerations.
Umbilical artery Doppler
• >32+0 weeks if reversed umbilical artery EDF
• >34+0 weeks if absent umbilical artery EDF
Maternal indications
• Local protocol, e.g. severe pre-eclampsia, HELLP syndrome
Delivery criteria met:
Delivery after steroid administration
Delivery criteria not met:
Repeat surveillance every 2 days