29th World Congress on Ultrasound in Obstetrics and Gynecology

12-16 October 2019
Berlin, Germany

Ultrasound Obstet Gynecol 2017; **50:** 285–290
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.18815

Editorial

Severe fetal growth restriction at 26–32 weeks: key messages from the TRUFFLE study

C. M. BILARDO[1], K. HECHER[2], G. H. A. VISSER[3], A. T. PAPAGEORGHIOU[4], N. MARLOW[5], B. THILAGANATHAN[4], A. VAN WASSENAER-LEEMHUIS[6], T. TODROS[7], K. MARSAL[8], T. FRUSCA[9], B. ARABIN[10], C. BREZINKA[11], J. B. DERKS[12], A. DIEMERT[2], J. J. DUVEKOT[13], E. FERRAZZI[14], W. GANZEVOORT[15], P. MARTINELLI[16], E. OSTERMAYER[17], D. SCHLEMBACH[18], H. VALENSISE[19], J. THORNTON[20], H. WOLF[15] and C. LEES[21]*, on behalf of the TRUFFLE Group[#]

[1]*Fetal Medicine Unit, Department of Obstetrics and Gynecology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands;* [2]*Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [3]*University Medical Center, Division of Woman and Baby, Utrecht, The Netherlands;* [4]*St George's, University of London and St George's University Hospitals NHS Foundation Trust, Molecular and Clinical Sciences Research Institute, London, UK;* [5]*Department of Academic Neonatology, UCL Institute for Women's Health, London, UK;* [6]*Department of Neonatology, Emma Children's Hospital Academic Medical Centre, Amsterdam, The Netherlands;* [7]*Department of Obstetrics & Gynecology, University of Turin, Turin, Italy;* [8]*Department of Obstetrics and Gynecology, Lund University, University Hospital, Lund, Sweden;* [9]*Maternal-Fetal Medicine Unit, University of Parma, Parma, Italy;* [10]*Department of Perinatology, Isala Clinics, Zwolle, The Netherlands, and Center for Mother and Child of the Philipps University, Marburg, Germany;* [11]*Department of Obstetrics and Gynecology, Medical University Innsbruck, Innsbruck, Austria;* [12]*Perinatal Center, Wilhelmina Children's Hospital, Utrecht, The Netherlands;* [13]*Division of Obstetrics and Prenatal Medicine, Department of Obstetrics and Gynaecology, Erasmus MC, Rotterdam, The Netherlands;* [14]*Buzzi Children's Hospital, University of Milan, Milan, Italy;* [15]*Department of Obstetrics and Gynecology, Academic Medical Centre, Amsterdam, The Netherlands;* [16]*Department of Gynecology and Obstetrics, University Federico II of Naples, Naples, Italy;* [17]*Section of Perinatal Medicine, Department of Obstetrics and Gynecology, Technical University, Munich, Germany;* [18]*Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria;* [19]*Department of Biomedicine, Tor Vergata University, Policlinico Casilino, Rome, Italy;* [20]*Department of Obstetrics and Gynaecology, City Hospital, Nottingham, UK;* [21]*Department of Surgery and Cancer, Imperial College London, London, UK, and Department of Development and Regeneration, KU Leuven, Leuven, Belgium*
**Correspondence. (e-mail: christoph.lees@nhs.net)*

What was the TRUFFLE study?

The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) was a prospective, multicenter, unblinded, randomized trial that ran between 1 January 2005 and 1 October 2010 in 20 European centers[1]. It studied singleton pregnancies at 26–32 weeks of gestation with a diagnosis of fetal growth restriction (FGR), defined as abdominal circumference < 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, the 503 included women were randomly allocated to one of three 'timing-of-delivery' plans (with 1 : 1 : 1 randomization).

What were the three timing-of-delivery arms?

Women were randomized to one of three groups that mandated delivery based on either:

(1) reduced STV ('CTG-STV' group): abnormal CTG, defined as fetal heart rate STV < 3.5 ms between 26 + 0 and 28 + 6 weeks of gestation or STV < 4 ms between 29 + 0 and 31 + 6 weeks' gestation; in this group, DV measurements were not obtained;
(2) early changes in DV waveform ('DV-p95' or 'early-DV' group): DV-PI > 95th percentile; or CTG-STV below a 'safety-net' level (see box);
(3) late changes in DV waveform ('DV-no-A' or 'late-DV' group): DV A-wave (the deflection within the venous waveform signifying atrial contraction) at or below the baseline, i.e. indicating no or reversed flow; or CTG-STV below the same safety net as that for the DV-p95 group (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 should be an integral part. In addition, delivery could be indicated in any group based on maternal conditions (chiefly, pre-eclampsia).

#The TRUFFLE Group collaborating authors are listed at the end of the article.

Safety-net criteria for triggering delivery regardless of randomized group

STV criteria

Absolute indications for delivery in all randomized arms:

Cut-off 'rescue' value for delivery based on CTG at 26 + 0 to 28 + 6 weeks is STV < 2.6 ms
Cut-off 'rescue' value for delivery based on CTG at 29 + 0 to 31 + 6 weeks is STV < 3 ms
Delivery is triggered irrespective of STV if there are spontaneous repeated persistent unprovoked decelerations on CTG.

Umbilical artery Doppler criteria

Absolute indications for delivery in all randomized arms:

≥ 32 + 0 weeks: deliver if umbilical artery end-diastolic flow is reversed
≥ 34 + 0 weeks: deliver if umbilical artery end-diastolic flow is absent
Delivery may be undertaken according to local policies after 30 + 0 weeks if there is reversed umbilical artery end-diastolic flow, and after 32 + 0 weeks if there is absent umbilical artery end-diastolic flow.

What were the results for the primary outcome of the randomized trial?

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

There are two ways in which to evaluate the primary outcome. One is to assess 'survival without neurological impairment'; in this composite outcome, death is, in a sense, equivalent to neurological impairment. There was no significant difference in this outcome among all pregnancies randomized. However, because neurological assessment is only possible in surviving infants, the protocol specified a second way to evaluate the outcome, in which the primary analysis is restricted to the surviving infants. This is also justifiable on the grounds that it is an outcome important to parents. In this analysis, there were statistically significantly more neurologically intact 2-year-old babies in the group randomized to late DV changes (or due to the CTG-STV safety net) compared with those randomized to CTG: the proportion without neurodevelopmental impairment at 2 years was 85% in the CTG-STV group, 91% in the early-DV group and 95% in the late-DV 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].

What were the other findings of the TRUFFLE study?

The median gestational age at delivery was 30.7 (interquartile range (IQR), 29.1–32.1) weeks and the mean birth weight was 1019 (SD, 322) g, confirming the severe early-onset FGR in the women taking part. Despite this severity, outcomes were better than those often reported: over 80% of babies survived and had no demonstrable neurological impairment at 2 years of age; 12 (2%) fetuses died *in utero* despite close monitoring; and 27 (6%) neonatal deaths occurred. The cerebral palsy rate was around 1%, much lower than that frequently quoted. Nearly three-quarters of women developed gestational hypertension. The interval from inclusion to delivery varied widely (median, 8; IQR, 3–17 days). The interval was significantly shorter in women who had pre-eclampsia at inclusion (median, 4; IQR, 2–10 days) than in those who did not (median, 12; IQR, 5–20 days). Other parameters, such as allocation group, gestational age, estimated fetal weight and umbilical artery Doppler findings, did not affect this interval significantly.

Figure 1 shows the proportion of babies which survived with no impairment or with impairment and those which died, both overall and according to gestational age at recruitment at 26 + 0 to 28 + 6 and 29 + 0 to 31 + 6 weeks[2].

Were TRUFFLE babies a highly selected sample?

Early-onset FGR is not common, so in that sense, yes. However, after excluding fetuses affected by congenital abnormalities, chromosomal conditions or infections (based on a careful ultrasound scan, chromosomal testing when indicated and a blood infection screen), most had FGR due to uteroplacental insufficiency. These investigations are all carried out routinely in European fetal medicine settings and are applicable to any such setting. It should be noted that there was a group of cases with even more severe early FGR which 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 applied with caution in such fetuses.

Are the TRUFFLE results generalizable?

The results are generalizable in settings in which there are specialist fetal medicine experts with the ability to undertake arterial and venous Doppler assessments regularly, in which computerized CTG (cCTG) is available and in which there are high-level neonatal facilities.

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

The better-than-expected outcomes probably reflect the benefit of being in a trial and being looked after closely by expert obstetric teams and having expert neonatal care. These outcomes suggest that clinical care in early-onset FGR should be undertaken in tertiary-level units. It has been shown in many studies that joining trials is of benefit (even in those in which an intervention proves ineffective)[3].

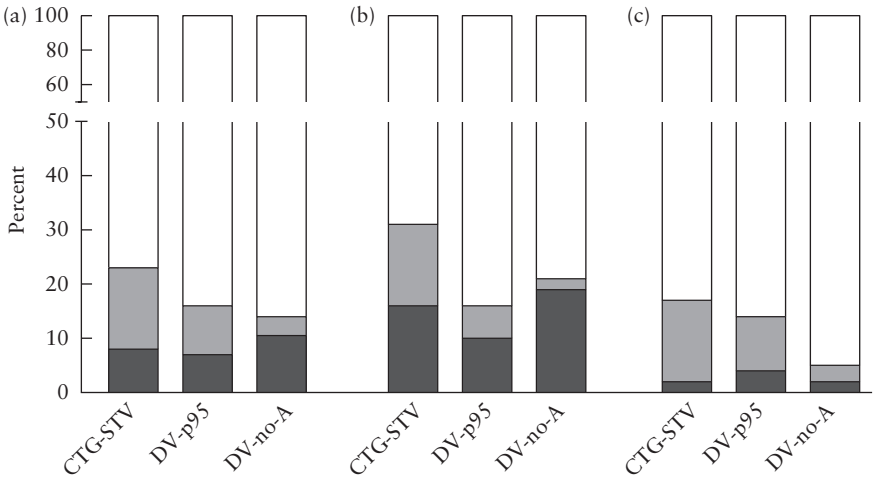

Figure 1 Proportion of babies with known outcome at 2 years in each of the three randomization groups which survived with no impairment (□), which survived with impairment (▩) and which died (■): (a) overall and (b,c) according to gestational age at recruitment, at 26 + 0 to 28 + 6 weeks (b) or at 29 + 0 to 31 + 6 weeks (c). Groups were randomized according to timing of delivery, based on: short-term variation on cardiotocography (CTG-STV); early changes in ductus venosus (DV) waveform, i.e. DV pulsatility index > 95th percentile (DV-p95); or late changes in DV waveform, i.e. DV A-wave at or below the baseline (DV-no-A).

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 group delivered on late DV changes consisted of a package, which included cCTG at 'safety-net' level alongside DV Doppler. It should be noted that, in the DV Doppler groups, twice as many fetuses were delivered on the basis of the CTG safety-net criteria than were delivered due to DV changes. Moreover, the somewhat poorer outcome in the CTG-STV group might be explained by the absence of a DV safety net in that group, whereas the DV Doppler groups had a cCTG safety net. One should expect outcomes similar to those of the TRUFFLE study only by using DV Doppler and cCTG in conjunction.

My hospital does not use cCTG. Can I use normal CTG?

We do not recommend this. The CTG monitoring in the TRUFFLE study was based on computerized assessment of fetal heart STV. Although there is no randomized trial evidence against visual interpretation, cCTG is the only objective measure of fetal heart rate that has been validated against invasive testing in fetal hypoxemia and acidemia. Simple visual interpretation of a regular CTG may not be sufficiently informative or sufficiently objective to provide reassurance about the fetal condition. The cCTG equipment used calculated STV based on the Dawes–Redman algorithm. cCTG 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 FGR[4], these have not yet been evaluated for clinical management.

Given the current interest in the cerebral circulation, should we deliver based on middle cerebral artery PI, cerebroplacental ratio or umbilical artery/middle cerebral artery PI ratio?

No. There were weak associations between middle cerebral artery (MCA) Doppler and short-term neonatal outcome, and between MCA Doppler and umbilical:cerebral 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' gestation[5].

Did neurodevelopmental impairment change with gestational age and was it related to neonatal morbidity?

An important strength of the TRUFFLE study is that babies were followed up to the age of 2 years, allowing assessment of neurodevelopmental impairment. The overall rate was 10%. Although neonatal morbidity was a risk factor, in most infants with neurodevelopmental impairment this was not preceded by morbidity[6] (Figure 2).

But many women in the two DV Doppler groups 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 mandated by 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,

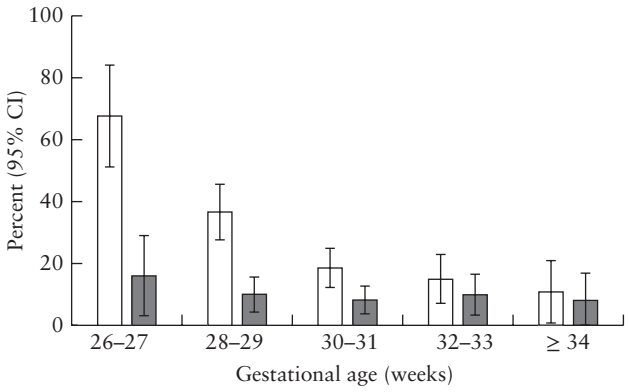

Figure 2 Bar chart showing rates, according to gestational age, of severe neonatal morbidity (□) (a composite of one or more of the following severe morbidities: bronchopulmonary dysplasia, severe germinal matrix cerebral hemorrhage Grade III or IV, cystic periventricular leukomalacia, proven neonatal sepsis, necrotizing enterocolitis) and of neurodevelopmental impairment at 2 years (■) (a composite of one or more of the following: cognitive Bayley-III score < 85, disabling cerebral paresis, hearing loss requiring hearing aid, severe visual loss) in surviving children. There were 31 children delivered at 26–27 weeks, 109 delivered at 28–29 weeks, 145 delivered at 30–31 weeks, 80 delivered at 32–33 weeks and 37 delivered ≥ 34 weeks. There was a significant relationship between neonatal morbidity and gestational age ($P < 0.001$), but not between neurodevelopmental impairment and gestational age ($P = 0.40$). Adapted from Van Wassenaer-Leemhuis *et al.*[6]. ©2017 Royal College of Obstericians and Gynaecologists.

analyzing according to the intended delivery criteria rather than the actual reason for delivery. This is because when the decision is made to monitor an individual woman with a certain modality, it is not known which factors will intercede in the future. Of course, many women were delivered according to protocol before 32 weeks, and this included those delivered for cCTG safety-net indication in the early- and late-DV groups. We have detailed these outcomes[7]: there was a lower rate of survival without neurodevelopmental impairment in those randomized to CTG (which included umbilical artery but not DV Doppler) than in mothers delivered according to DV changes. The finding that many women deliver for reasons other than DV changes means that CTG, which was an integral part of all three arms, is a key component of the monitoring strategy and should not be disregarded.

What about the fact that there were more fetal deaths in the late-DV group? And why were neurodevelopmental outcomes better in survivors within the DV Doppler groups?

There were 12 fetal deaths in total, two in the CTG-STV group, four in the early-DV group and six in the late-DV group; it is likely that the differences in number of fetal deaths between groups occurred by chance. Fetal deaths were categorized as unexpected or due to planned non-intervention. All unexpected deaths occurred in the DV Doppler groups (three in the early- and four in the late-DV group). The other five antenatal deaths were inevitable (parents declined intervention)[8]. Assessment of the monitoring parameters that were obtained shortly before demise in the cases of unexpected fetal death showed an abnormal CTG in only one. Hence, six of the seven cases would not have been delivered if they had been allocated to the CTG-STV group. The pathophysiological reason why neurodevelopmental outcomes were better in the DV Doppler groups is not elucidated by the TRUFFLE study. However, we speculate that both CTG-STV and DV Doppler are parameters that indicate different (failing) homeostatic mechanisms. As the sequence of these changes may vary between fetuses, a combination of both parameters could be more effective in determining the moment when the balance of the risks associated with intervention and with expectant management slides towards favoring intervention.

What were the findings in fetuses delivered < 32 weeks?

This was the best defined group of the study since delivery > 32 weeks was undertaken according to local protocols. Outcomes prior to 32 weeks, as for delivery after 32 weeks, were significantly better in those women randomized to monitoring by DV compared to the CTG group[7,8], with no differences between the two DV subgroups. Hence, combined DV and CTG (safety net) monitoring seems to be the best way forward in managing these cases. So, delivery is indicated if DV becomes abnormal or if CTG safety-net criteria are met. 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 abnormalities. It is also important to bear in mind that CTG safety net includes the occurrence of spontaneous decelerations and/or low cCTG-STV values. As the optimum level of the cCTG-STV cut-off value was not tested in the study, the cCTG-STV values adopted as safety-net values may be used.

How often should we monitor early FGR?

There is no international consensus on the optimal frequency of monitoring in early FGR. Although the TRUFFLE protocol specified that DV and CTG should be monitored at least weekly, most centers (17 of 20) performed cCTG at least daily. A longitudinal analysis of these data in women delivered before 32 weeks demonstrated that for each day the median risk for a very low STV or recurrent decelerations (DV Doppler groups' safety-net criteria) was 5% (IQR, 4–7%)[9]. It is suggested that daily monitoring contributed to the good outcomes seen in this study; however, the frequency of monitoring in relation to outcome was not tested in the RCT.

How can I use the TRUFFLE results for counseling?

The two bar charts in Figure 3, taken from the TRUFFLE report of perinatal morbidity and mortality analyzed

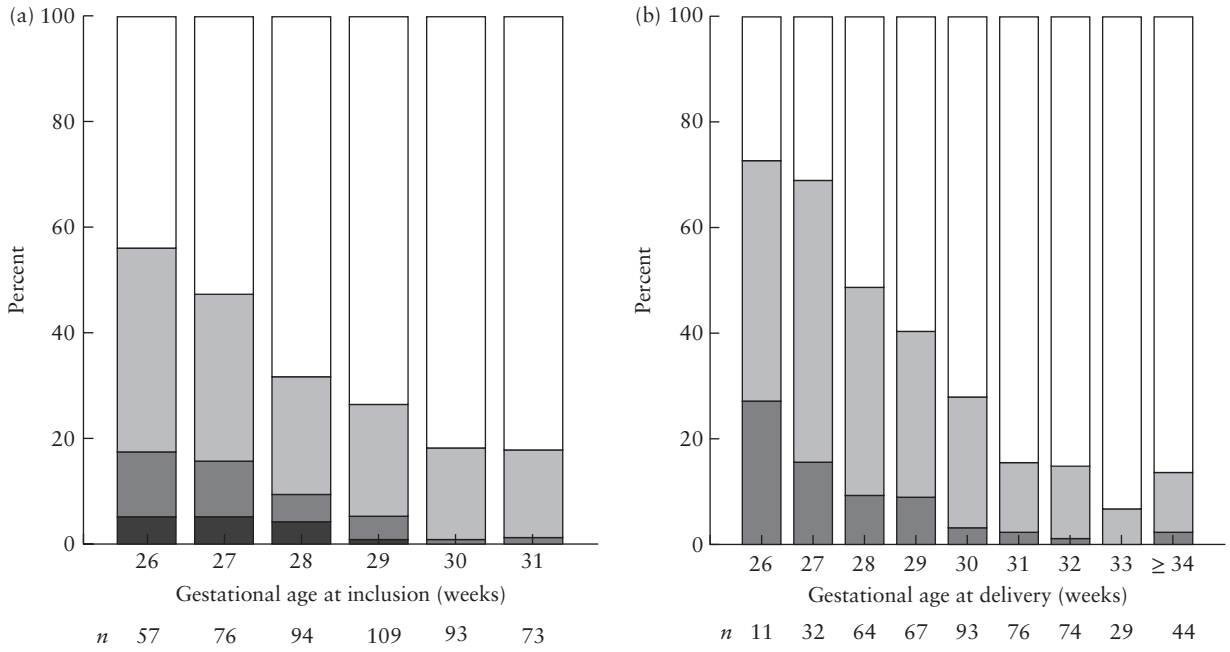

Figure 3 Outcome for: (a) fetuses ($n=502$) according to gestational age at inclusion; (b) live births ($n=490$) according to gestational age at delivery. '*n*' row indicates total number of infants represented in each bar (one case is missing). Severe morbidity is defined as bronchopulmonary dysplasia, severe germinal matrix cerebral hemorrhage Grade III or IV, cystic periventricular leukomalacia of more than Grade I, proven neonatal sepsis or necrotizing enterocolitis. □, No severe morbidity; ▒, severe morbidity; ■, neonatal death; ■, fetal death.

as a cohort[2], may be useful in counseling. They give the main outcome data, according to gestational age, for counseling women both at study inclusion and at delivery. For example, if a woman is diagnosed with FGR, the bar chart 'at inclusion' (Figure 3a) is used. If her pregnancy proceeds a further few weeks and there is a plan to deliver, the chart 'at delivery' (Figure 3b) can be used to update the counseling.

How often should we monitor maternal blood pressure?

The TRUFFLE study did not evaluate the optimal frequency of blood pressure monitoring. However, it was found that, in 70% of cases of FGR, the mother developed gestational hypertensive morbidity. It would therefore 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 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 the umbilical artery end-diastolic flow was reversed, at 34 weeks if it was absent, and beyond 34 weeks if the umbilical artery PI was raised. Delivery for the same criteria at 30 weeks, 32 weeks and beyond 32 weeks, respectively, was discretionary.

As the upper gestational age at recruitment to TRUFFLE study was 31 + 6 weeks, the TRUFFLE study cannot answer the question as to how best to monitor and when to deliver these slightly older babies. The TRUFFLE 2 randomized study, currently under development, will test different triggers for delivery in women with compromised and/or small babies at 32–37 weeks (www.truffle-study.org).

How should we interpret the primary and secondary results of the TRUFFLE study?

Overall, when restricted to survivors, the outcome was significantly better in the late-DV compared with the CTG-STV group. Secondary analysis, restricted to surviving infants delivered before 32 weeks who were managed according to the study protocol, showed no difference in the primary outcome between the DV Doppler groups. Combining both DV Doppler groups pre-32 weeks showed a significantly better outcome compared with the CTG-STV group (relative risk, 0.91 (95% CI, 0.83–1.00); number needed to treat, 13)[7,8].

TRUFFLE data provide evidence that management of pregnancies in which there is early-onset FGR in a tertiary-level perinatal center and DV Doppler measurement in conjunction with cCTG improves long-term infant outcome; a flowchart explaining the recommended protocol is shown in Figure 4. DV measurement is not very time-consuming. Our advice, therefore, is to include DV Doppler measurement with cCTG for the monitoring of women with early-onset FGR. It is unlikely that further randomized data will become available in the near future.

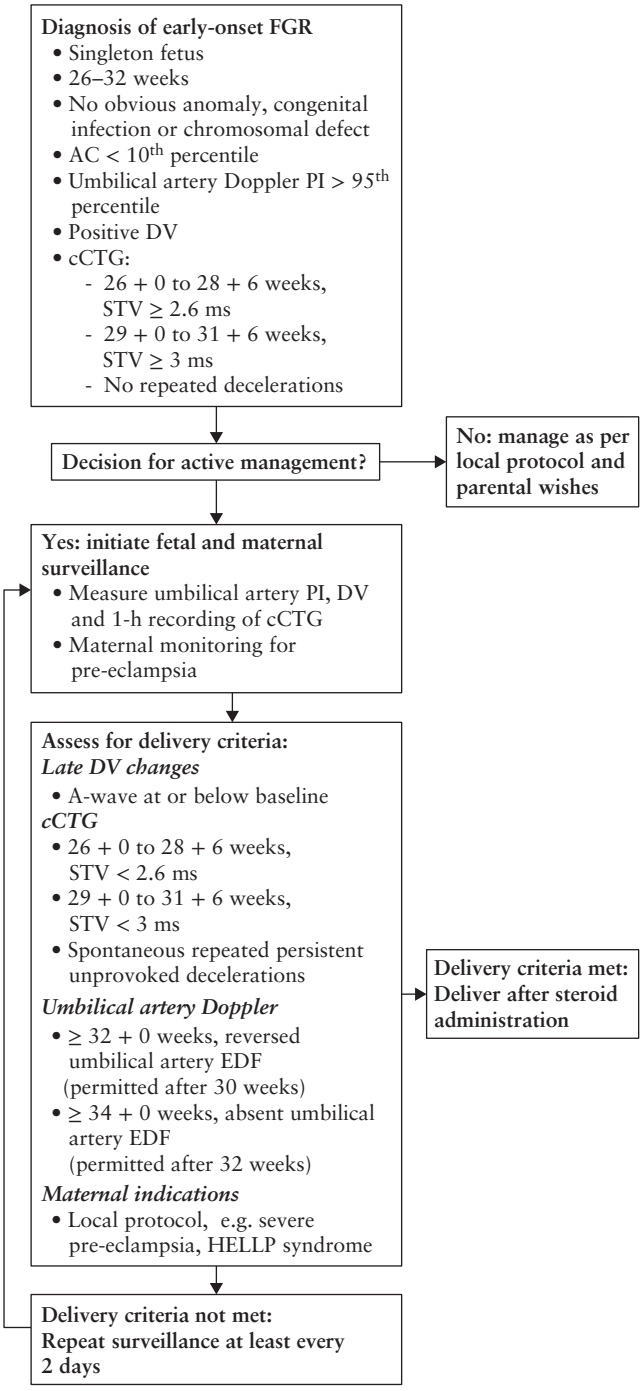

Figure 4 Flowchart explaining protocol recommended by TRUFFLE study for monitoring and management of pregnancies with an early diagnosis of fetal growth restriction (FGR). AC, abdominal circumference; cCTG, computerized cardiotocography; DV, ductus venosus; EDF, end-diastolic flow; PI, pulsatility index; STV, short-term variation.

TRUFFLE GROUP COLLABORATING AUTHORS

P. Calda, Prague, Czech Republic; S. Gordjin, Groningen, The Netherlands; W. Gyselaers, Genk, Belgium; P. Klaritsch, Graz, Austria; S. Lobmaier, Munich, Germany; M. Manz, Hamburg, Germany; R. Napolitano, London, UK; F. Prefumo, Brescia, Italy; R. Schild, Hannover, Germany; T. Stampalija, Trieste, Italy; C. von Holsbeke, Genk, Belgium; C. von Kaisenberg, Hannover, Germany.

REFERENCES

1. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H; TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomized trial. *Lancet* 2015; **385**: 2162–2172. [Erratum: Lancet 2015; 385: 2152.]
2. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvekot J, Frusca T, Diemert A, Ferrazzi E, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcamonico A, Visser GH, Wolf H; TRUFFLE Group. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* 2013; **42**: 400–408.
3. Nijjar SK, D'Amico MI, Wimalaweera NA, Cooper N, Zamora J, Khan KS. Participation in clinical trials improves outcomes in women's health: a systematic review and meta-analysis. *BJOG* 2017; **124**: 863–871.
4. Lobmaier SM, Mensing van Charante N, Ferrazzi E, Giussani DA, Shaw CJ, Müller A, Ortiz JU, Ostermayer E, Haller B, Prefumo F, Frusca T, Hecher K, Arabin B, Thilaganathan B, Papageorghiou AT, Bhide A, Martinelli P, Duvekot JJ, van Eyck J, Visser GH, Schmidt G, Ganzevoort W, Lees CC, Schneider KT; TRUFFLE investigators (see Acknowledgments). Phase-rectified signal averaging method to predict perinatal outcome in infants with very preterm fetal growth restriction - a secondary analysis of TRUFFLE-trial. *Am J Obstet Gynecol* 2016; **215**: 630.e1–7.
5. Stampalija T, Arabin B, Wolf H, Bilardo CM, Lees C; TRUFFLE investigators. Is middle cerebral artery Doppler related to neonatal and 2-year infant outcome in early fetal growth restriction? *Am J Obstet Gynecol* 2017; **216**: 521.e1–13.
6. Van Wassenaer-Leemhuis AG, Marlow N, Lees C, Wolf H; TRUFFLE investigators. The association of neonatal morbidity with long-term neurological outcome in infants who were growth restricted and preterm at birth: secondary analyses from TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe). *BJOG* 2017; **124**: 1072–1078.
7. Visser GHA, Bilardo CM, Derks JB, Ferrazzi E, Fratelli N, Frusca T, Ganzevoort W, Lees CC, Napolitano R, Todros T, Wolf H, Hecher K, on behalf of the TRUFFLE group investigators. Fetal monitoring indications for delivery and 2-year outcome in 310 infants with fetal growth restriction delivered before 32 weeks' gestation in the TRUFFLE study. *Ultrasound Obstet Gynecol* 2017; **50**: 347–352.
8. Ganzevoort W, Mensing van Charante N, Thilaganathan B, Prefumo F, Arabin B, Bilardo CM, Brezinka C, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Hecher K, Marlow N, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider K, Todros T, Valcamonico A, Visser G, van Wassenaer-Leemhuis A, Lees CC, Wolf H, for the TRUFFLE Group. How to monitor pregnancies complicated by fetal growth restriction and delivery before 32 weeks: *post-hoc* analysis of TRUFFLE study. *Ultrasound Obstet Gynecol* 2017; **49**: 769–777.
9. Wolf H, Arabin B, Lees CC, Oepkes D, Prefumo F, Thilaganathan B, Todros T, Visser GH, Bilardo CM, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Hecher K, Marlow N, Martinelli P, Ostermayer E, Papageorghiou AT, Scheepers HC, Schlembach D, Schneider KT, Valcamonico A, van Wassenaer-Leemhuis A, Ganzevoort W, on behalf of the TRUFFLE group. Longitudinal study of computerized cardiotocography in early fetal growth restriction. *Ultrasound Obstet Gynecol* 2017; **50**: 71–78.

