The TRUFFLE study; fetal monitoring indications for delivery in 310 IUGR infants with 2 year's outcome delivered before 32 weeks of gestation

Gerard H.A.Visser (1), C.M Bilardo (2), J.B.Derks (1), E Ferrazzi (3), N.Fratelli (4), T. Frusca (5), W. Ganzevoort (6), C.Lees (7), R. Napolitano (8), T.Todros (9), H.Wolf (6), K.Hecher (10) on behalf of the TRUFFLE group investigators*

1 Department of Perinatology, University Medical Center, Utrecht, Netherlands

2 Department of Obstetrics and Gynaecology, University Medical Center, University of Groningen, Netherlands

3 Department of Woman, Mother and Neonate, Buzzi Children's Hospital, University of Milan, Milan, Italy

4 Maternal-Fetal Medicine Unit, University of Brescia, Brescia, Italy

5 Department of Obstetrics and Gynecology, University Hospital, Parma, Italy

6 Department of Obstetrics and Gynecology, Academic Medical Centre, Amsterdam, Netherlands

7 Department of Surgery and Cancer, Imperial College London, London, UK; and Department of Development and Regeneration, KU Leuven, Leuven, Belgium

8 Department of Gynecology and Obstetrics, University Federico II of Naples, Naples, Italy

9 Department of Obstetrics and Gynecology, Sant' Anna Hospital, Turin, Italy

10 Department of Obstetrics and Fetal Medicine, University Medical Center, Hamburg-Eppendorf, Germany

*TRUFFLE group investigators: N Marlow (11) , B Arabin (12) , C Brezinka (13), A Diemert (10), JJ Duvekot (14), P Martinelli (7), E Ostermayer (15), AT

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.17361

Papageorghiou (16), D Schlembach (17), KTM Schneider (15), B Thilaganathan (16), A Valcamonico (4)

11 Department of Neonatology, UCL Institute for Women's Health, London, UK

12 Center for Mother and Child of the Phillips University, Marburg, Germany

13 Obstetrics and Gynecology, Universitatsklinik fur Gynakologische Endokrinologie und Reproduktionsmedizin, Department fur Frauenheilkunde, Innsbruck, Austria

14 Department of Obstetrics and Gynaecology, Erasmus MC, Rotterdam, Netherlands

15 Division of Perinatal Medicine, Department of Obstetrics and Gynecology, Technical University, Munich, Germany

16 Department of Obstetrics, St George's, University of London, London, UK

17 Department of Obstetrics, Friedrich Schiller University of Jena, Jena, Germany

TRUFFLE group collaborators: A Aktas (Marburg), S Borgione (Turin), R Chaoui (Berlin), JMJ Cornette (Rotterdam), T Diehl (Hamburg), J van Eyck (Zwolle), IC van Haastert (Utrecht), J Kingdom (Toronto), S Lobmaier (Munich), E Lopriore (Leiden), H Missfelder-Lobos (Cambridge), G Mansi (Naples), P Martelli (Brescia), G Maso (Trieste), K Marsal (Lund), U Maurer-Fellbaum (Graz), N Mensing van Charante (Amsterdam), S Mulder-de Tollenaer (Zwolle), M Oberto (Turin), D Oepkes (Leiden), G Ogge (Turin), JAM van der Post (Amsterdam), F Prefumo (Brescia/London), L Preston (Cambridge), F Raimondi (Naples), H Rattue (London), IKM Reiss (Rotterdam), LS Scheepers (Nijmegen/Maastricht), A Skabar (Trieste), M Spaanderman (Nijmegen), J Thornton (Nottingham), H Valensise (Rome), N Weisglas–Kuperus (Rotterdam), A Zimmermann (Munich)

Key words: fetal growth restriction, cardiotocography, fetal heart rate variation, ductus venosus, preterm delivery

Abstract

Objective: In the TRUFFLE study on outcome of early fetal growth restriction women were allocated to three timing of delivery plans according to antenatal monitoring strategies based on reduced computerized cardiotocographic heart rate short term variation (c-CTG STV) , early Ductus Venosus (DV p95) or late DV (DV noA) changes. However, many infants were per protocol delivered because of 'safety net' criteria, or for maternal indications, or 'other fetal indications' or after 32 weeks of gestation when the protocol was not applied anymore. It was the objective of the present post-hoc sub-analysis to investigate the indications for delivery in relation to outcome at 2 years in infants delivered before 32 weeks, to come to a further refinement of management proposals.

Methods: we included all 310 cases of the TRUFFLE study with known outcome at 2 years corrected age and 7 perinatal and infant deaths, apart from 7 cases with an inevitable death. Data were analyzed according to the randomization allocation and specified for the intervention indication.

Results: overall only 32% of fetuses born alive were delivered according to the specified monitoring parameter for indication for delivery. 38% were delivered because of safety net criteria, 15% because of other fetal reasons and 15% because of maternal reasons. In the c-CTG arm 51% of infants were delivered because of reduced STV. In the DV p95 arm 34% were delivered because of an abnormal DV and in the DV no A wave arm only 10% of cases were delivered accordingly. The majority of fetuses in the DV arms delivered for safety net criteria were delivered because of spontaneous decelerations. Two year's intact survival was highest in the combined DV arms as compared to the c-CTG arm ($p=0.05$ when life born, $p= 0.21$ including fetal death), with no difference between the DV arms. Poorer outcome in the c-CTG arm was restricted to fetuses delivered because of decelerations in the safety net subgroup. Infants delivered because of maternal reasons had the highest birth weight and a non-significant higher intact survival.

Conclusions: In this sub-analysis of fetuses delivered before 32 weeks the majority of infants were delivered for other reasons than according to the allocated CTG or

DV monitoring strategy. Since in the DV arms CTG criteria were used as safety net criteria, but in the c-CTG arms no DV safety net criteria were applied, we speculate that the slightly poorer outcome in the CTG arm might be explained by absence of DV data. Optimal timing of delivery of the early IUGR fetus may therefore best be achieved by monitoring them longitudinally with DV and CTG monitoring.

Introduction

The 2 year outcome data of the TRUFFLE study(' Trial of Umbilical and Fetal Flow in Europe') on outcome of early intrauterine growth restricted (IUGR) fetuses has shown that overall outcome of these fetuses was more favourable than published in the past (1). Timing of delivery was randomized and based on reduced computerized cardiotocograph heart rate short term variation (c-CTG STV), and early or late pulsatility changes in the Ductus Venosus (DV), with safety net criteria in all three intervention strategies.

Impaired outcome (mortality and severe morbidity) did not differ significantly between cases delivered in the three arms of the trial, but data on intact two year's neurological outcome showed that a conservative approach to the timing of delivery by waiting for late DV changes, was associated a better outcome in the survivors as compared to the c-CTG arm. Data were analysed according to intention to treat. However, a considerable proportion of infants was delivered per protocol because of co-called 'safety net' criteria (i.e. severely reduced c-CTG STV, occurrence of spontaneous unprovoked heart rate decelerations, or -after 30 weeks- because of reversed end-diastolic flow velocities (ReDV) in the umbilical artery, without abnormalities in DV flow velocity waveform patterns. Since cardiotocography is the standard of care in monitoring of IUGR fetuses at risk of impaired intra-uterine condition, c-CTG STV safety net criteria were established for patients randomized to the DV groups only, while DV was not evaluated in patients randomized to CTG monitoring. Moreover, in all 3 arms of

the trial many infants were delivered because of maternal indications or 'other fetal indications' or after 32 weeks of gestation, when delivery occurred according to local protocols and not according to the intention to treat arms of the protocol.

Therefore, there is the need for a post-hoc sub-analysis of the TRUFFLE data , especially for infants delivered before 32 weeks to investigate outcome at 2 years in relation to the indications for delivery, to come to a further refinement of management proposals.

Methods

In the multicenter, unblinded, randomized TRUFFLE study we included women with singleton fetuses at 26–32 weeks of gestation who had very preterm fetal growth restriction (ie low abdominal circumference [<10th percentile] and a high umbilical artery Doppler pulsatility index [>95th percentile]). We randomly allocated women 1:1:1, with randomly sized blocks and stratified by participating center and gestational age (<29 weeks vs ≥29 weeks), to three timing of delivery plans, which differed according to antenatal monitoring strategies: reduced c-CTG STV (STV <3.5 ms at <29 weeks of gestation or STV <4 ms at ≥29 weeks of gestation), early DV changes (pulsatility index >95th percentile; DV p95), or late DV changes (zero or reversed A wave; DV no A). The safety net c-CTG STV criteria as used in the two DV groups were set considerably lower than in the CTG STV arm, namely ≥26 - <29 weeks if STV < 2.6 and ≥30 - <32 weeks if STV< 3. Joint safety-net criteria for all three randomization arms included the occurrence of spontaneous decelerations and, after 30 weeks, reversed end-diastolic flow velocities (REDV) in the umbilical artery. The primary outcome was survival without cerebral palsy or neurosensory impairment, or a Bayley III developmental score of more than 85, at 2 years of age. This study was registered with ISRCTN, number 56204499. Between January 2005 and October 2010 503 women were included. Results on direct neonatal and 2 year's outcome have been published before (1,2).

In this post-hoc sub-analysis we included all 310 live born cases of the TRUFFLE study with known outcome at 2 years corrected age, that were delivered before 32 weeks of gestation and 7 fetal deaths. Cases in which it was refrained from intervention before birth because of suspected poor prognosis of the infant (n=5)

and 2 cases born with a lethal congenital malformation were not included (2) . There were 25 neonatal deaths that were included in the analyses. Most of the analyses were made on the 310 life born cases. However, for comparison with the data from the original TRUFFLE study and where appropriate, data are also shown for 2 year's survivors only. Data were analyzed according to the randomization allocation specified for the intervention indication. Data were analysed by anova or chi-square test as appropriate, using IBM SPSS version 22 (New York, USA).

Results

We included 310 infants born alive before 32 weeks of gestation and 7 fetal deaths. The number of infants born alive according to randomization arm and intervention indication is shown in Table 1. Overall two-third of the infants were delivered according to the specified criteria of the randomization strategies. Slightly more than half of these were delivered because of safety net criteria. The remaining one-third of the study population was delivered because of other off-protocol fetal indications or for maternal indications.

In the c-CTG STV arm 54 of 104 infants (51%) were delivered because of reduced STV. In 19 of these cases also decelerations were present. In the DV arms delivery because of a DV>95th centile was the reason for delivery in 34% of cases allocated to that arm and in the DV no A wave arm only 10% of cases were delivered for absent or reversed A-wave. In the latter group over 50% of cases were delivered because of safety net criteria and almost 40% because of other fetal or maternal indications. The 7 fetal deaths occurred in the latter two groups (3 in the DV P95 and 4 in the DV no A wave group).

The supplementary Table shows gestational age and weight at delivery according to randomization and indication for delivery. There were no significant differences between the subgroups, although birth weight was higher in infants

delivered for maternal indications (anova, corrected for multiple tsting, p=0.02), while gestational age was similar, as compared to the other indication groups .

Outcome at 2 years is shown in Table 2. Overall 83% of live born infants were alive without neurological impairment at 2 years of age. This percentage was 86 for infants delivered in both DV arms and 77 for those delivered in the c-CTG arm (p=0.049for live born infants if comparing CTG-STV to both DV groups combined). There were 7 fetal deaths, all in the DV arms. When these deaths were included, intact outcome in the DV arms decreased to 83% (p=0.21 when compared to the CTG arm). Overall the most favourable outcome (92%) occurred in infants delivered because of maternal reasons and this held for all 3 randomization arms (p=0.09 for maternal versus all other indications, excluding fetal death). The lowest incidence of intact outcome (15 of 26; 58%) occurred in the infants in the CTG arm delivered because of safety net criteria. Outcome in this group was significantly poorer than that in the DV arms in which delivery took place on the basis of safety net criteria (p=0.001) . In fact, the poorer outcome in the CTG arm was only due to a poorer outcome in the safety net subgroup. There was no difference in 2 year's outcome between infants that were delivered based on the c-CTG STV criteria (favourable outcome in 44 of 54; 82%), as compared to those delivered based on DV criteria (combined group n=45, favourable outcome in 36, 80%).

Results were similar when the 25 neonatal deaths were excluded. In the c-CTG arm 81 of 95 survivors (85%) had a normal neurological outcome, as compared to 176 of 190 (93%) in the combined DV groups (Table 2; p=0.049). The lowest incidence of intact survival occurred in the infants in the c-CTG group delivered because of safety net (15 of 22 (68%), versus 80 of 85 in the combined DV groups (94%)), with no differences in intact survival in case delivery was based on the specified CTG abnormality in the c-CTG arm (44 of 50; 88%) or DV abnormality in the combined DV arms (36 of 41; 88%).

Table 3 shows a sub-division of the safety net criteria according to the randomization arms. Low STV was only a safety net criterium in the DV groups. The other criteria held for all 3 groups (joined criteria). 67% of infants in the

safety net group were delivered because of decelerations, 12% because of a low STV, another 15 % because of a combination of both and only 6% because of ReD velocities in the umbilical artery at a gestational age >30 weeks. In the combined DV arms very low STV alone was an indication for delivery in only 14 out of 92 cases (15%) and a very low STV combined with decelerations in another 18 cases (20%); decelerations, with or without low STV were by far the most important determinant for delivery in the DV arms (79%). When delivery was indicated by decelerations then adverse 2-year infant outcome was significantly more frequent in the CTG-STV arm than in the DV-groups (p=0.003). For the other safety net criteria outcome was not significantly different from the overall 2-year infant outcome. (Table 3), although all 7 cases delivered because of ReDV in the umbilical artery after 30 weeks did well.

In 19 of the 54 cases in the CTG arm delivered because of STV criteria (Table 1) also decelerations were present. In a further 24 only decelerations were present (Table 4). In other words, in the CTG arm slightly more fetuses were delivered because of reduced STV than because of decelerations.

When leaving out infants delivered because of maternal reasons, ReD flow umb art or off-protocol (i.e infants in which there were no recorded CTG or DV abnormalities), altogether 210 infants were delivered because of CTG (STV +decelerations) or DV abnormalities. 165 of these infants were delivered because of CTG and 45 because of DV. Of the infants delivered because of an abnormal DV, 80 % were normal at follow-up (36 of 45) and that held for 83% delivered because of CTG abnormalities. (132 of 165).

The only fetuses monitored with both CTG and DV, were those in the two DV arms. Even in these arms twice as many infants (n=87) were delivered because of CTG safety net STV and/or decelerations than because of DV changes (n=45). Slightly more infants delivered because of CTG were normal at follow-up (75 of 87, 86%; see Table 3), as compared to 80% delivered because of DV (36 of 45; see Table 3). So these data indicate that overall outcome of infants delivered because of CTG changes was at least similar to those delivered because of DV

abnormalities. Only in the subgroup, monitored with only c-CTG without DV, outcome was poorer.

Discussion

We have performed a post-hoc sub-analysis of outcome of infants from the TRUFFLE trial who were delivered before 32 weeks of gestation. By doing so we excluded infants born _>32 weeks, who were likely to be at lower risk for impaired outcome and were delivered according to local management criteria and not according to the initial randomization arms (1). This analysis was done to obtain more insight in 2 year's outcome in relation to the actual indications for delivery. A disadvantage of the smaller size of this study was the fact that it was not powered for the questions raised. Conclusions have, therefore, to be drawn with caution.

We found that 2 year's outcome was better in the DV arms as compared to the CTG arm and this is in line with that of the total study population (1). In the original TRUFFLE study primary outcome, i.e. survival without CP or neurosensory impairment, was not significantly different between the randomization arms, but neurological outcome in survivors was significantly better in the DV no A wave arm as compared to that in the CTG arm, with a trend towards better outcome in the DV>95th centile arm.

When specified for the actual indication for delivery (specified CTG or DV abnormality, safety net, other fetal indications, maternal indications) we found no differences between groups in two year's outcome, although those delivered for maternal indication had a non-significantly better outcome. The latter may be related to a significantly higher birth weight at the same age at delivery.

In the DV no A group more fetuses were delivered because of other fetal indications or maternal indications, than in the other arms of the trial. The reason is unclear also since ''other fetal indications'' was not specified enough by the participating centers, apart from cases with partial placental abruption. Waiting for late DV changes may have increased the chance for CTG and other fetal indications to arise.

The better outcome in the DV groups appears initially somewhat difficult to explain given the fact that only 35 and 10% of infants in the DV p95 and DVnoA arm, respectively, were actually delivered because of the allocated DV abnormalities, whereas 52 and 73 %, respectively, were delivered because of safety net or other fetal indications. The safety net criteria largely relate to the occurrence of fetal heart rate decelerations or a very reduced STV, i.e. CTG criteria. Altogether more infants in the DV arms were delivered on the basis of CTG safety net criteria than on the basis of an abnormal ductus flow velocity pattern. This implies that in the majority of cases CTG abnormalities (STV and/or decelerations) preceded DV changes. From longitudinal studies it is known that c-CTG STV and DV changes occur more or less at the same time in early IUGR fetuses (3,4). In other words in half of the cases changes in c-CTG STV precede DV changes, but also the opposite holds true. The differences in outcome may, therefore, be related to the study design in which in the DV groups CTG safety net criteria were included, whereas in the CTG arm no DV measurements were obtained. From earlier studies we know that survival in early IUGR is higher if either CTG or DV anomalies had been present as compared to cases in which both had been abnormal (3,4,5). The poorer outcome in the c-CTG group may therefore, be due to the fact that in this arm in a substantial number of cases both CTG and DV abnormalities had been present.

Outcome of fetuses in the CTG arm delivered on the basis of c-CTG STV was identical to that of those delivered in the combined DV arms on the basis of DV abnormalities. It therefore seems essential to include c-CTG when determining the timing of delivery. The significantly poorer outcome in the CTG safety net group delivered because of decelerations, as compared to the DV arms delivered because of this criterion, may well indicate, that absence of knowledge on DV in this subgroup has delayed delivery and has been causal to the poorer outcome. In this context it has to be realized the TRUFFLE study was a comparison of CTG monitoring only, with combined DV and CTG monitoring. Our data stress the importance of monitoring early IUGR fetuses with both CTG and DV.

In clinical practice this implies that when monitoring early IUGR fetuses with both techniques, the majority will be delivered because of CTG abnormalities before DV changes occur. DV may therefore be considered the ''safety net'' for CTG monitoring. Such a safety net seems useful, also since the data from the original TRUFFLE trial and the ones from the present sub-analysis have shown that monitoring with CTG alone (without a DV safety net), resulted in a poorer outcome, than when combining both assessment techniques.

STV threshold values for normality may not be clear at this moment. We have defined normal STV as a STV > 3.5 ms in between 26-28 weeks of gestation and > 4 in between 29 till 32 weeks (1). These threshold values were set taken into account the increase in STV with increasing gestational age (6,7), the absence of fetal acidaemia in case of a STV>4 ms (8) and presence of acidaemia or hypoxaemia in the majority of cases when STV was in between 3.5-4 ms (9). The 2.5^{th} centile of STV in normal populations has been found to be around 4-5 ms in the early third trimester in recordings of variable length (10) or around 4.4-5.4 in CTG recordings of one hour duration (6,7). Therefore, we have used a lower STV threshold values in the present study. However, it is known that fetal heart rate decelerations occur on average at the same time as heart rate variation falls below the normal range (11) . Since in the present study slightly more fetuses in the c-CTG arm were delivered on the basis of reduced STV than because of decelerations, it seems unlikely that the STV threshold values in the CTG arm were set too low.

The fact that most fetuses in the DV arms that were delivered on safety net indications were delivered on the basis of decelerations and not on the applied

very low STV cut-off values, suggests that the latter values might have been set too low. Therefore, it may be that the same criteria used in the c-CTG arm should be used. The more so since outcome in the c-CTG arm of fetuses delivered according to the specified monitoring parameter, was identical to that of cases delivered in the DV arms because on an abnormal DV. However, the optimal STV cut-off values might be subject to further analysis. The more so, since we had no information on DV in the c-CTG arm and it may therefore be that cases with a reduced STV according to the c-CTG arm might have been identified by DV abnormalities. It should also be noted that the TRUFFLE STV threshold values were based on one hour CTG recordings. Shorter recordings may give less accurate results (1,2,6). Moreover, possible effects of medication like betamethasone and MgSO4 should be taken into account, since both drugs may reduce STV without affecting the occurrence of declelerations (12-16).

Taken into account the restriction that the present post-hoc sub-analysis was not powered for the questions raised in this paper, the present data suggest some refinement in the management protocol of early IUGR fetuses delivered before 32 weeks of gestation:

1- the optimal timing of delivery may best be achieved by combined longitudinal monitoring using both c-CTG and DV. Given that low STV (<2.6 before 29 weeks and <3 between 30 and 32 weeks) do not appear to be associated with an increase in adverse outcome and it may be safe to wait for such abnormalities to occur as long as DV remains normal.
2- The favourable outcome in the small group of fetuses delivered because of reversed end-diastolic velocities in the umbilical artery after 30 weeks of gestation, supports the use of this criterion after this gestational age.

The data from this sub-analysis based on the actual indications for delivery in infants delivered before 32 weeks of gestation, support those of the whole TRUFFLE study, whereby it has to be realised that almost 2/3rd of cases will be delivered per protocol because of other indications than CTG in the c-CTG arm, or abnormal DV in the DV arms. This held especially for fetuses allocated to the DV arms. Overall, outcome of IUGR fetuses delivered before 32 weeks, appears to be

better than historical data have shown and this is likely to be due to the close multi-modality (Doppler and c-CTG) monitoring.

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 GHA, Wolf H; TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. The Lancet 2015; 385:2162–2172.

2-Lees CC, 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 GHA, 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 Gynaecol, 2013;42:400–408

3-Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackelöer BJ, Kok HJ, Senat MV, Visser GHA. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol, 2001;18:564–570

4- Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, Battaglia FC, Galan HL Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol, 2002; 19:140–146.

5- Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, Germer U, Moyano D, Turan S, Hartung J, Bhide A, Müller T, Bower S, Nicolaides KH, Thilaganathan B, Gembruch U, Ferrazzi E, Hecher K, Galan HL, Harman CR. Predictors of neonatal outcome in early-onset placental dysfunction Obstet Gynecol. 2007;109:253-261

6- Nijhuis IJM , ten Hof J, Mulder EJH, Nijhuis JG, Narayan H, Taylor DJ, Visser GHA. Numerical fetal heart rate analysis: nomograms, minimal duration of recording and intrafetal consistency Pren Neon Med 1998;3:314-322

7- Nijhuis IJM, ten Hof J, Mulder EJH, Nijhuis JG, Narayan H, Taylor DJ, Visser GHA. Fetal heart rate in relation to its variation in normal and growth retarded fetuses. Eur J Obstet Gynecol Reprod Biol. 2000;89:27-33

8- Dawes GS, Moulden M, Redman CWG. Short-term fetal heart rate variation, decelerations, and umbilical flow velocity waveforms before labor Obstet Gynecol 1992;80:673-678

9- Ribbert LSM, Snijders RJM, Nicolaides KH, Visser GHA. Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses. Brit.J Obstet Gynaecol 1991;98:820-823

10- Serra V Bellver J, Moulden M, Redman CWG. Computerized analysis of normal fetal heart rate pattern throughout gestation. Ultrasound Obstet Gynecol 2009; 34: 74–79.

11- Snijders RJM, Ribbert LSM**,** Visser GHA, Mulder EJH. Numeric analysis of heart rate variation in intrauterine growth-retarded fetuses: a longitudinal studyAm J Obstet Gynecol 1992;166:22-27

12- Mulder EJH, Derks JB, Visser GHA. Antenatal corticosteroid therapy and fetal behaviour: a randomised study of

the effects of betamethasone and dexamethasone Br J Obstet Gynaecol. 1997;104:1239-1247#

13- Multon O[1], Senat MV, Minoui S, Hue MV, Frydman R, Ville Y. Effect of antenatal betamethasone and dexamethasone administration on fetal heart rate variability in growth-retarded fetuses. Fetal Diagn Ther 1997;12:170-177

14- Frusca T, Soregaroli M, Valcamonico A, Scalvi L, Bonera R, Bianchi U. Effect of betamethasone on computerized cardiotocographic parameters in preterm growth-restricted fetuses with and without cerebral vasodilation. Gynecol Obstet Invest. 2001;52:194–197.

15- Nensi A, De Silva DA, von Dadelszen P, Sawchuck D, Synnes AR, Crane J, Magee LA. Effect of magnesium sulphate on fetal heart rate parameters: a systematic review. J Obstet Gynaecol Can. 2014;36:1055-64.

16- Hiett AK, Devoe LD, Brown HL, Watson J. Effect of magnesium on fetal heart rate variability using computer analysis. Am J Perinatol. 1995;12:259-61.

Table 1: Number of infants born alive (n=310) before 32 weeks of gestation according to randomization arm (intention to treat) and intervention indication. ReDV: Reversed end-diatolic velocities umbilical artery.

	c-CTG STV	DV p95	DV no A	All
Indication for delivery:				
According to randomization arm:				
-Specified CTG or DV abnormality	54	34	11	99 (32%)
-Safety net, total	26	37	55	118 (38%)
-DV STV safety net criteria*		11	21	
-Joint safety net criteria:				
Spontaneous decel	24	22	33	
ReDV >30 weeks	2	4	1	
Other fetal indications	9	15	22	46 (15%)
Maternal	16	13	18	47 (15%)
Total	105	99	106	310

*STV<2.6 before 29 weeks and <3 after 29 weeks

Table 2: Number of infants with normal neurological follow-up and total number with known outcome, specified for the indication of delivery and randomization allocation. Selected were only infants delivered before 32 weeks, fetal death due to inevitable poor prognosis and neonatal death due to a lethal anomaly were excluded. In 'total including fetal death' the 7 antepartum deaths were included and in 'total, survivors only' outcome in the 285 survivors is shown

Indication for delivery	**c- CTG STV**	**DV p95**	**DV no A**	**All**
According to randomization arm:				
- Specified CTG or DV abnormality	44/54 (82%)	26/34 (77%)	10/11 (91%)	80/99 (81%)
- Safety-net	15/26 (58%)	34/37 (92%)	46/55 (84%)	95/118 (81%)
Other fetal indications*	7/9 (78%)	14/15 (93%)	18/22 (82%)	39/46 (85%)
Maternal	15/16 (94%)	11/13 (85%)	17/18 (94%)	43/47 (92%)
Total, liveborn infants with known outcome	81/105 (77%)	85/99 (86%)	91/106 (86%)	257/310 (83%)
Total incl. fetal death	81/105 (77%)	85/102 (83%)	91/110 (83%)	257/317 (81%)
Total, survivors only	81/95 (85%)	85/93 (91%)	91/97 (94%)	257/285 (90%)

*including 8 cases of partial abruption (2, 2 and 4, respectively; all these infants did well)

Table 3: Sub-division of safety net criteria for randomization allocation for infants with normal or abnormal neurological follow-up at 2 year's of age and total number. ReDV= reversed end-diastolic velocities umbilical artery

Safety-net indications for delivery	**c-CTG STV**	**DV p95**	**DV no A**	**Total**
Low STV* only	-	2	12	14
Normal outcome	-	1	9	(71%)
Abnormal outcome	-	1	3	
Decelerations only	24	22	33	79
Normal outcome	13	20	27	(76%)
Abnormal outcome	11	2	6	
Low STV* with decelerations	-	9	9	18
Normal outcome	-	9	9	(100%)
Abnormal outcome	-	0	0	
ReDV only > 30 weeks	2/2	4/4	1/1	7
Normal outcome	2	4	1	(100%)
Abnormal outcome	0	0	0	
Total	26	37	55	118
Normal outcome	15 (58%)	34 (92%)	46(84%)	(81%)
Abnormal outcome	11 (42%)	3 (8)	9 (16%)	

* DV group only

Supplementary Table : Median gestational age and weight of infants born alive (n=310) before 32 weeks of gestation according to randomization arm and intervention indication (fetal death excluded).

Indication for delivery	N	c-CTG		DV p95		DVnoA		All	
N		105		99		106		310	
		GA	BW	GA	BW	GA	BW	GA	BW
Specified CTG or DV abnormality	99	29.5 (28.6 to 30.9)	901 (198)	29.4 (28.1 to 30.6)	832 (208)	29.9 (28.6 to 30.9)	851 (275)	29.6 (28.6 to 30.9)	872 (211)
Safety net	118	29.9 (28.4 to 30.6)	832 (175)	30.0 (28.6 to 31.2)	881(221)	29.9 (28.7 to 30.7)	885 (221)	29.9 (28.6 to 30.9)	872 (211)
Other fetal indications	46	30.0 (28.9 to 30.7)	851 (180)	30.3 (29.0 to 31.1)	932 (183)	30.4 (29.2 to 31.0)	875 (139)	30.3 (29.0 to 31.0)	889 (162)
Maternal	47	29.8 (27.9 to 31.4)	956 (251)	30.0 (29.3 to 30.9	1019 (258)	29.8 (28.0 to 30.7)	901 (198)	29.9 (28.4 to 31.0)	952 (234)
All	310	29.7 (28.5 to 30.9)	888 (202)	29.9 (28.7 to 31.0)	890 (222)	29.9 (28.7 to 30.8) (	882 (207)	29.9 (28.7 to 30.9)	887 (209)