26 Fetal Doppler Velocimetry in High-Risk Pregnancies: Randomized Clinical Trials

Christoph C. Lees and T. Stampalija

26.1 Introduction

Doppler technology has spread progressively with advances in ultrasound machines' performance, operators' training, and better understanding of the physiopathology of the feto-placental circulation in pathologies such as fetal growth restriction, hypertensive disorders in pregnancy, and twin pregnancies among others. For example, the cascade of Doppler changes in early fetal growth restriction, caused by uteroplacental insufficiency, and its association with an adverse perinatal outcome is now well-known [1–3]. The identification of hypoxia and acidemia constitutes the rationale for using Doppler ultrasound as one of the main tools for fetal well-being assessment and management in fetal growth restriction [4, 5]. Similarly, the management of monochorionic twin pregnancy [6] or fetal anemia [7] is unthinkable without Doppler ultrasound assessment of specific vascular domains. Although not universally adopted, Doppler of the uterine arteries, first applied in the mid-trimester [8, 9], represents one of the main components of first-trimester screening of preterm pre-eclampsia and fetal growth restriction [10, 11]. Hence, the application of Doppler ultrasound in high-risk pregnancies has become a standard clinical practice worldwide.

On the other hand, multiple Doppler interrogations of vascular districts may also cause false-positive findings, consequent unnecessary interventions, and potential adverse outcomes such as prematurity and patient and physician anxiety. Last but not least, for some widespread Doppler ultrasound applications, such as the assessment of the middle cerebral artery in fetal growth restriction, there is no high-quality evidence for its value, leading to variable clinical practice and management.

In this chapter, we will summarize the evidence from randomized clinical trials on Doppler velocimetry in high-risk pregnancies with a particular focus on fetal growth restriction and the effect of its application on maternal and fetal outcomes.

C. C. Lees (✉)
Department of Metabolism, Digestion and Reproduction, Imperial College Hospitals NHS Trust, London, UK

Centre for Fetal Care, Queen Charlotte's and Chelsea Hospital, Imperial College Hospitals NHS Trust, London, UK
e-mail: christoph.lees@nhs.net

T. Stampalija
Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy

Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy
e-mail: tamara.stampalija@burlo.trieste.it

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26.2 Trials of Umbilical Artery Doppler in High-Risk Pregnancies

26.2.1 Evidence from Randomized Studies

The Cochrane Systematic Review and meta-analysis on randomized and quasi-randomized controlled trials on fetal and umbilical Doppler ultrasound in high-risk pregnancies [12] reported 18 studies that compared the use of umbilical artery Doppler with no-Doppler (or Doppler not revealed to clinicians). In 14 studies, umbilical artery Doppler was used in addition to the standard fetal monitoring strategy [13–26], whereas in 4 studies, umbilical artery Doppler was evaluated compared to cardiotocography [27–30]. Table 26.1 shows the characteristics of the included studies in this meta-analysis. It should be noted that two of the included studies evaluated the Doppler of the umbilical and uteroplacental arteries [19, 26]: one evaluated the Doppler of the umbilical artery and aorta [21] and the other evaluated the middle cerebral to umbilical artery velocity flow systolic/diastolic ratio [23].

The pooled data of the use of umbilical artery Doppler ultrasound in high-risk pregnancies showed fewer perinatal deaths (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.52–0.98, 16 studies, 10,225 babies, 1.2% versus 1.7% number needed to treat (NNT) 203, 95% CI 103–4352, evidence graded as moderate) [12]. The findings for stillbirths and neonatal deaths were similar, showing fewer adverse outcomes in the Doppler group, although these did not reach statistical significance (stillbirth: RR 0.65, 95% CI 0.41–1.04, 15 studies, 9560 babies, evidence graded as low; neonatal deaths: RR 0.81, 95% CI 0.53–1.24, 8167 babies, 13 studies) [12]. Only three studies reported relevant neonatal morbidity data [19, 22, 26]. However, the heterogeneity was high and the quality of evidence extremely low, making the analysis uncertain [12].

Moreover, the use of umbilical artery Doppler was associated with fewer inductions of labor and fewer cesarean sections (induction of labor: RR 0.89, 95% CI 0.80–0.99, 10 studies, 5633 women, evidence graded as moderate; cesarean section: RR 0.90, 95% CI 0.84–0.97, 14 studies, 7918 women, evidence graded as moderate) [12]. Data for serious neonatal morbidity could not be pooled due to high heterogeneity between the studies. Finally, although not a pre-specified outcome, there were fewer antenatal admissions in the Doppler group (RR 0.72, 95% CI 0.60–0.88, 839 women, 2 studies) [12].

Four trials [27–30] compared the umbilical artery Doppler assessment with cardiotocography assessment. However, for this comparison, there was insufficient evidence to detect a significant difference in perinatal mortality.

In summary, as presented in Table 26.2, these data suggest that the use of umbilical artery Doppler ultrasound, with or without cardiotocography, in high-risk pregnancies reduces the risk of perinatal deaths and reduces obstetric interventions compared to no-Doppler [12].

However, it has to be acknowledged that this meta-analysis included all pregnancies defined to be at a higher risk of fetal compromise, such as fetal growth restriction, post-term pregnancies, multiple pregnancies, previous pregnancy loss, women with hypertension, women with diabetes or other maternal pathologies. When a subgroup analysis was performed (i.e., only singleton or multiple or only small for gestational age or fetal growth restriction), there was no evidence of the treatment effect. There are five randomized controlled trials that assessed Doppler in the umbilical artery versus no-Doppler ultrasound in women with suspected small-for-gestational-age/growth-restricted fetuses [18, 20, 24, 27, 28]; only one study assessed the role of Doppler ultrasound in the umbilical artery versus no-Doppler ultrasound in pregnancies complicated by hypertension or pre-eclampsia [24] and only one study assessed the role of Doppler ultrasound in the umbilical artery versus no-Doppler ultrasound in women with previous pregnancy loss [22]. There were no significant differences in terms of perinatal mortality in the treatment group versus that in the no-treatment group (small-for-gestational-age/fetal growth restriction group: RR 0.72, 95% CI 0.38–1.35, 1292 women, 5 studies; hypertensive disorders in pregnancy group: RR 3.57, 95%

Table 26.1 Characteristics of the included studies in the cochrane meta-analysis (adapted from Alfirevic et al. 2017) [12]

Study	Participants	Number of participants	Intervention	Comparison	Outcomes	Notes
Almstrom, 1992 [27]	Singleton pregnancies with suspected FGR at 31 completed gestational weeks	427	Doppler of the umbilical artery only	CTG only	Primary: GA at delivery, frequency of CS, vacuum, forceps, operative delivery for fetal distress, length of stay at the NICU Secondary: number of fetal monitoring occasions, duration of antenatal hospital stay, frequency of labor induction, birth weight, frequency of small-for-date infants, Apgar score at 1 min and 5 min, need for respiratory support	
Biljan, 1992 [13]	High-risk singleton pregnancies	674	Doppler of the umbilical artery	No-Doppler	Elective births; GA at birth; birth weight; Apgar scores, admissions to the NICU, length of time in the NICU, number of babies ventilated, length of ventilation, perinatal mortality	Poster presentation
Burke, 1992 [14]	High-risk pregnancies (suspected FGR, HDP, previous birth weight <2.5 kg, antepartum hemorrhage, previous perinatal death, diminished fetal movements, post-maturity, diabetes, and others)	476	Doppler of the umbilical artery, fetal biometry, and BPP scoring	Fetal biometry and BPP scoring	Induction of labor, elective and emergency CS, preterm delivery, and perinatal loss	
De Rochambeau, 1992 [15]	Singleton post-term pregnancies	107	Doppler of the umbilical artery	No-Doppler	CS, RDS, and post-maturity	

(continued)

Table 26.1 (continued)

Study	Participants	Number of participants	Intervention	Comparison	Outcomes	Notes
Giles, 2003 [16]	Twin pregnancies (monochorionic and dichorionic) at 25 weeks	539	Doppler of the umbilical artery and biometry at 25, 30, and 35 weeks; advised to undertake interventions if there was an abnormal umbilical artery Doppler (>95th centile S/D ratio) or abnormal biometry, indicating discordant growth. The suggested intervention was intensive surveillance by obstetric caregivers; if other indicators of fetal well-being (lack of serial growth, decreased amniotic fluid or abnormal fetal monitoring) were abnormal, then early delivery was advised >25 weeks; an abnormality of Doppler waveforms themselves was not considered an indication for immediate delivery unless there was an absence of diastolic flow velocity at >32 weeks	Biometry at 25, 30, and 35 weeks	Maternal: antenatal admission, presence of hypertension, gestation at delivery, indication for delivery, and mode of delivery Fetal: biometry measurements, umbilical artery Doppler systolic diastolic ratios and the occurrence of fetal death and causative factors Neonatal: birth weight, Apgar scores, admission to NICU, admission to special care nursery, requirements for ventilation, and occurrence of neonatal death (up to 28 days of life)	
Haley, 1997 [28]	Singleton pregnancies at risk of FGR >26 weeks	150	Only Doppler of the umbilical artery	Only CTG	Duration of hospital antenatal admission, induction of labor rate; number of investigations (CTG or Doppler), number of outpatient visits to hospital, emergency CS rate, length of stay in the NICU, birth weight and 1 min and 5 min Apgar score; women views on their care	
Hofmeyr, 1991 [29]	Women of a high-risk obstetric unit	867	Doppler of the umbilical artery	cCTG	Number and duration of tests; perinatal outcomes	

Johnstone, 1993 [17]	Pregnancies identified clinically as being at increased risk	2289	Doppler of the umbilical artery and standard monitoring (CTG/BPP)	Standard monitoring (CTG/BPP)	Fetal mortality and morbidity; obstetric interventions; use of other tests of fetal monitoring; impact on obstetric decision-making; health and personal costs; women's satisfaction	
Neals, 1994 [18]	Singleton pregnancy with FGR >24 weeks	467	Doppler of the umbilical artery revealed	Doppler of the umbilical artery concealed	Obstetric management: gestation at birth, time from enrolment to birth, mode of birth/onset of labor, fetal distress in labor Neonatal outcome: perinatal mortality, birth weight, admission to the NICU, neonatal outcome	Personal communication
Newnham, 1991 [19]	High-risk pregnancies, singleton and twins, stratified for twins	505	Doppler of the umbilical and uteroplacental (within the placental bed) arteries	No-Doppler	Primary: duration of neonatal stay in hospital Secondary: number and type of fetal heart monitoring studies, obstetric interventions, frequency of fetal distress, birth weight, Apgar score, and need for a NICU	
Nienhuis, 1997 [20]	Singleton pregnancies at risk of FGR	161	Doppler of the umbilical artery revealed	Doppler of the umbilical artery concealed	Effect on costs in terms of hospitalization, perinatal outcome, neurological development and postnatal catch-up growth, onset and mode of birth, birth weight and GA at birth	
Nimrod, 1992 [21]	Women post-term (>40 weeks)		Doppler of the umbilical artery and fetal aorta revealed, BPP and CTG	Doppler of the umbilical artery and fetal aorta concealed, BPP and CTG	CS; gestation at birth; meconium in amniotic fluid; need for phototherapy	Conference abstract
Norman, 1992 [22]	High-risk pregnancies with recurrent pregnancy loss (two or more mid-trimester or early third-trimester losses, which resulted in IUFD, stillbirth or neonatal death) >24 weeks	564	Doppler of the umbilical artery revealed	Doppler of the umbilical artery concealed	Maternal intervention, hospital stay, induction of labor, CS, perinatal mortality and morbidity	Conference abstract

(continued)

Table 26.1 (continued)

Study	Participants	Number of participants	Intervention	Comparison	Outcomes	Notes
Ott, 1998 [23]	High-risk pregnancies (risk of uteroplacental insufficiency, fetal risk, post-dates, maternal diabetes, PROM/PTL and fluid abnormalities)	715	Fetal and umbilical artery Doppler, modified BPP	Modified BPP	Primary outcome: neonatal morbidity rate (admission to the NICU, length of stay in the NICU, significant neonatal morbidity) Secondary outcome: GA at delivery, neonatal weight, CS for fetal distress	
Pattison, 1994 [24]	Singleton pregnancies with HDP and/or SGA >28 weeks	212	Doppler of the umbilical artery revealed and standard care	Doppler of the umbilical artery concealed and standard care	Perinatal mortality and morbidity, antenatal hospitalization, maternal intervention, admission to the NICU, and hospitalization until discharge from the neonatal wards	
Trudinger, 1987 [25]	Singleton high-risk pregnancy >28 weeks	300	Doppler of the umbilical artery revealed and standard care	Doppler of the umbilical artery concealed and standard care	Perinatal mortality, CS, induction of labor	
Tyrell, 1990 [26]	Singleton pregnancies at risk of FGR or stillbirth	500	Doppler of the umbilical and uteroplacental arteries, BPP and other tests	Doppler of the umbilical and uteroplacental arteries and BPP revealed only on special request (n = 12 women), only other tests	Total number of days of antenatal admission, rate of induction of labor (by any method), mode of birth (elective and emergency CS), 1 and 5 min Apgar, birth weight, admission to the NICU	
Williams, 2003 [30]	Singleton high-risk pregnancies: FGR 7%, HDP 10%, diabetes 11%, prolonged pregnancy 43%, decreased fetal movements 22%, >32 weeks	1360	Doppler of the umbilical artery: if Doppler is normal, then women seen twice a week; if equivocal, then amniotic fluid index done; if abnormal, then proceeded to induction/delivery within 24 h	Electronic FHR with NST: twice a week; Kulbi score (five components). If equivocal (identified Kulbi = 6), then assessment of amniotic fluid volume; if abnormal (identified Kulbi = 4), then induction/delivery within 24 h	Primary outcome: incidence of CS for fetal distress in labor (non-reassuring FHR) Secondary outcome: total CS, Apgar score 1 and 5 min, the incidence of stillbirth, the presence of meconium and the incidence of transfer to the NICU with severe neonatal morbidity	

FGR fetal growth restriction, *CTG* cardiotocography, *GA* gestational age, *CS* cesarean section, *NICU* neonatal intensive care unit, *HDP* hypertensive disorders in pregnancy, *BPP* biophysical profile, *IUFD* intrauterine fetal demise, *PROM* preterm rupture of membranes, *PTL* preterm labor, *SGA* small for gestational age, *FHR* fetal heart rate, *NST* non-stress test

Table 26.2 Summary of the findings from a systematic review and meta-analysis of randomized controlled trials on the Doppler of the umbilical artery versus no-Doppler in high-risk pregnancies (adapted from Alfirevic et al. 2017) [12]

Outcome	Relative effect (95% CI)	Number of participants	Number of studies	Quality of evidence (GRADE)	Comments
Any perinatal death after randomization	RR 0.71 (0.52–0.98)	10,225	16	Moderate +++	
Serious neonatal morbidity		1098	3		Not possible to pool the data due to high heterogeneity
Stillbirth	RR 0.65 (0.41–1.04)	9560	15	Low ++	
Apgar <7 at 5 min	RR 0.92 (0.69–1.24)	6321	7	Low ++	
Cesarean section (elective and emergency)	RR 0.90 (0.84–0.97)	7918	14	Moderate +++	
Induction of labor	RR 0.89 (0.80–0.99)	5633	10	Moderate +++	

CI confidence interval, *RR* risk ratio

CI 0.42–30.73, 89 women, 1 study; previous pregnancy loss group: RR 0.26, 95% CI 0.03–2.17, 53 women, 1 study).

The lack of evidence in subgroup analysis might be due to several factors such as a small number of included cases, publication bias, and heterogeneity of the included studies. It is noteworthy that all studies were published more than 20 years ago, the reason being the fact that at present not performing umbilical artery Doppler in high-risk pregnancies would now be considered as unethical. Finally, the fact that the majority of the studies were performed in the 1990s, before the international agreement on how to report clinical trials [31], makes quality assessment of the older studies imprecise, and very few studies are graded as high-quality by today's standards.

The next question might be whether there is a specific group of high-risk pregnancies that benefits most from umbilical artery Doppler assessment. In order to answer this question, Westergaard et al. [32] performed a meta-analysis dividing the studies into "well-defined studies," i.e., studies that included pregnancies complicated by fetal growth restriction and/or hypertensive disorders in pregnancy, and "general risk studies," i.e., studies that included a variety of high-risk pregnancies. There were no statistically significant differences for perinatal mortality in both groups (well-defined studies: odds ratio (OR) 0.66, 95% CI 0.36–1.22; general risk studies: OR 0.68, 95% CI 0.43–1.08). However, an international experts' audit on perinatal deaths concluded that the use of Doppler in "well-defined studies" potentially might have prevented some. In the same group, there was a significant reduction in antenatal admissions, induction of labor, elective deliveries (induction and cesarean sections), and overall cesarean sections (OR 0.56, 95% CI 0.43–0.72; OR 0.78, 95% CI 0.63–0.96; OR 0.73, 95% CI 0.61–0.88 and OR 0.78, 95% CI 0.65–0.94, respectively). In conclusion, this meta-analysis suggests that pregnancies complicated by fetal growth restriction and/or hypertensive disorders in pregnancy would benefit most from umbilical artery Doppler assessment [32].

There are no randomized controlled trials on the umbilical artery in high-risk pregnancies, which evaluated long-term infant outcomes.

26.2.2 Implication for Practice

The findings from the first systematic review and meta-analysis of randomized controlled trials on fetal and umbilical artery Doppler in high-risk

pregnancies [33, 34], and subsequent updates [12, 35, 36], showed an improvement in perinatal outcomes and a reduction in operative deliveries. This led to the introduction of umbilical artery Doppler assessment in the management of high-risk pregnancies like fetal growth restriction [37]. The data from the meta-analysis of randomized trials suggest that the availability of umbilical artery Doppler in high-risk pregnancies allows for better timing of delivery to reduce the perinatal mortality and emergency cesarean sections, indicating a better identification of compromised babies before or during labor. This seems particularly true for cases with underlying placental insufficiency, such as fetal growth restriction and hypertensive disorders in pregnancy [32].

As a diagnostic test, umbilical artery Doppler is of importance for the diagnosis of fetal growth restriction and the distinction from small-for-gestational-age fetuses [38, 39], especially at the earlier gestational age epochs. However, it is still not completely clear which intervention, and when, should follow an abnormal umbilical artery Doppler finding in fetal growth restriction, with this being a crucial point in influencing the outcome. In fact, there are no randomized controlled clinical trials on delivery timing in fetal growth restriction based on umbilical artery Doppler. The same applies to the findings of absent or reverse end-diastolic flow in the umbilical artery. The latter findings reflect a more severe placental compromise [40] and are associated with higher perinatal morbidity and mortality [41]. However, there are no randomized controlled trials to support the optimum management protocol in these cases.

26.3 Trials of Ductus Venosus Doppler in High-Risk Pregnancies

26.3.1 Evidence from Randomized Studies

Abnormalities of the ductus venosus waveform are reported to be a good predictor of a perinatal outcome in early fetal growth restriction [1, 2, 42]. The alterations in ductus venosus flow, especially absent or reversed A-wave, represent late changes in the biophysical cascade of events in early fetal growth restriction, together with alterations of short-term variation and biophysical profile, preceding fetal acidemia, and intrauterine fetal demise [1–3]. It is believed that these changes in the ductal waveform are caused by progressive dilatation of the isthmus in an attempt to increase the blood flow toward the heart and to compensate for hypoxia [43, 44]. Thus, from the beginning, it has been clear that the assessment of the ductus venosus in early fetal growth restriction plays a crucial role. However, balancing delivery timing with prematurity is also of critical importance for perinatal and long-term outcomes [45–47]. This raises the question regarding the best biophysical tool and delivery timing in these fetuses.

The only randomized controlled trial that compared different biophysical tools in delivery decision-making in early fetal growth restriction is the TRUFFLE (TRial of Umbilical Fetal FLow in Europe) study [48, 49]. This trial involved 20 European centers and compared 3 interventional arms, early and late ductus venosus changes and short-term variation at computerized cardiotocography, as a trigger for delivery in singleton pregnancies with fetal growth restriction between 26 and 32 weeks of gestation in 503 women [49]. Fetal growth restriction was defined as an abdominal circumference below the tenth centile and an umbilical artery pulsatility index above the 95th centile. The three randomization interventional arms were as follows:

1. Early changes in the ductus venosus, defined as a pulsatility index above the 95th centile
2. Late changes in the ductus venosus, defined as absent or reverse A-wave
3. Reduced short-term variation, below 3.5 ms between 26^{+0} and 28^{+6} weeks of gestation and below 4 ms between 29^{+0} and 31^{+6} gestational weeks

There was a cardiotocography “safety net” for all three arms representing an absolute indication for delivery represented by:

- Spontaneous, repeated, persistent unprovoked decelerations in all three arms
- Short-term variation below 2.6 ms at 26^{+0}–28^{+6} weeks and below 3 ms at 29^{+0}–31^{+6} weeks in ductus venosus arms

The short-term variation "safety net" was deliberately set at a level below that of the cardiotocography arm (arm 3); hence, changes needed to be more extreme in the two ductus venosus groups. In addition, maternal conditions represented an indication for delivery in any group and at any gestational week. Figure 26.1 is the schematic representation of TRUFFLE randomization interventional arms and safety net.

The primary outcome of the TRUFFLE study was a 2-year survival without neurological impairment. The proportion among survivors without neurodevelopmental impairment at 2 years was 85% in the short-term variation group and 91% and 95% in early and late ductus venosus groups, respectively. A significant proportion of babies delivered in the late changes ductus venosus group was due to the short-term variation safety net criteria. Moreover, in the same group, there was a statistically non-significant increase in perinatal and infant mortality rate.

Overall, the results from the TRUFFLE study provided evidence that the timing of delivery based on ductus venosus Doppler measurement in conjunction with short-term variation "safety net" improves long-term (2-year neurodevelopmental) infant outcome in survivors [49]. Despite the fact that data from the TRUFFLE study showed better than assumed results in terms of survival without neurological impairment (overall, 82% of children), the gestational age at study entry and delivery and birth weight were strongly related to an adverse outcome as shown in Fig. 26.2.

26.3.2 Implication for Practice

Besides providing evidence for the best delivery trigger and timing in early fetal growth restriction

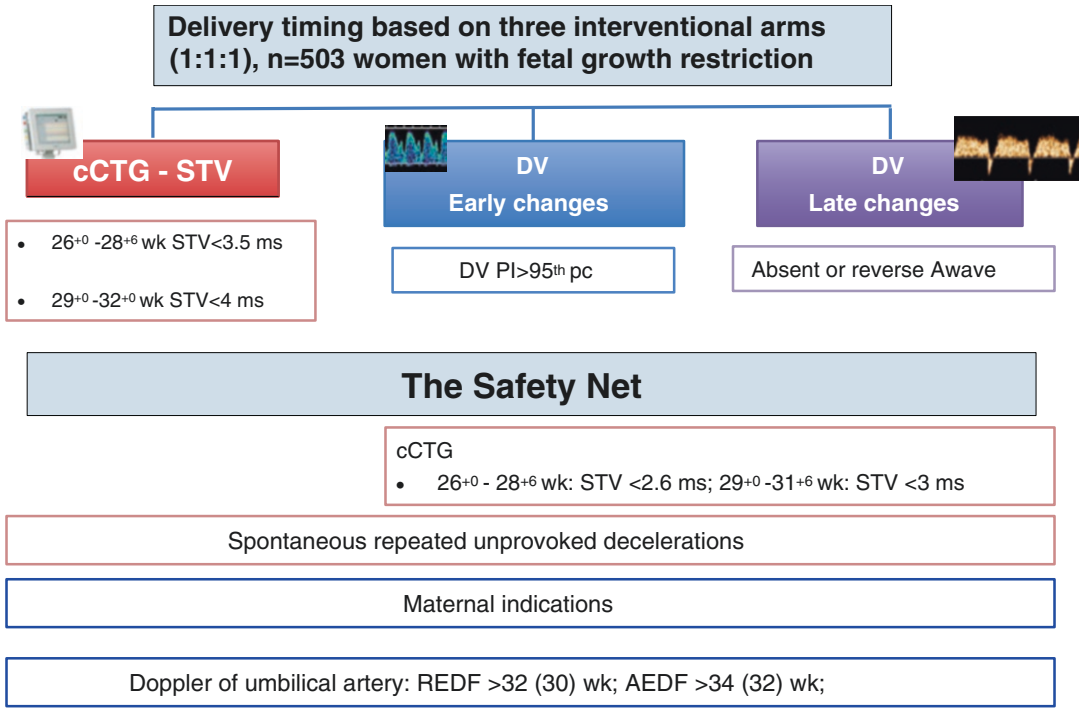

Fig. 26.1 Schematic representation of the TRUFFLE randomization interventional arms and safety net (adopted from Lees et al.) [48, 49]

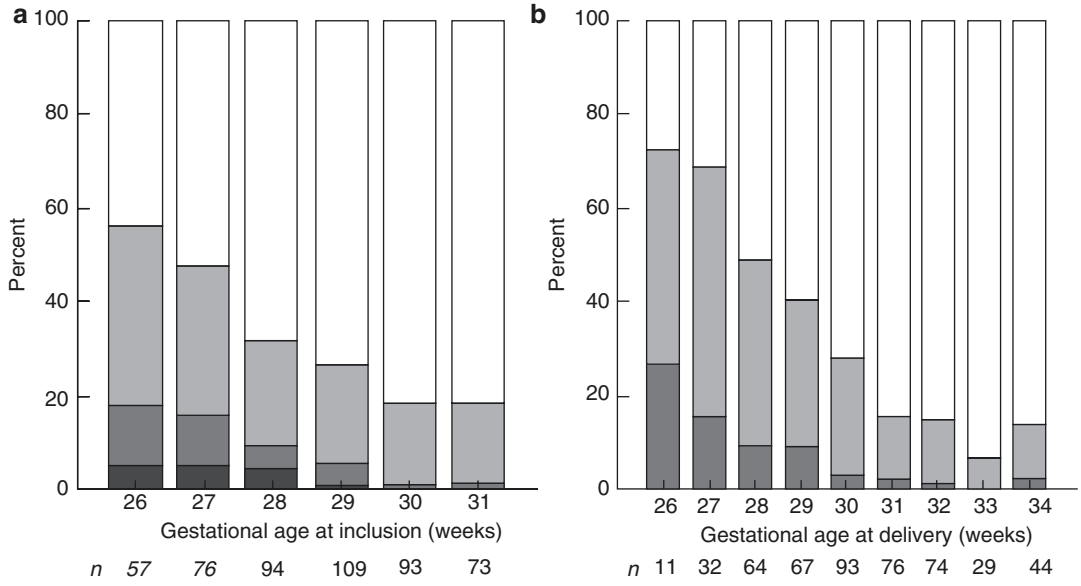

Fig. 26.2 Proportion of neonates without severe morbidity (white bars), with severe morbidity (light gray bars), neonatal death (dark gray bars), and fetal death (black bars) according to a) gestational age at inclusion and b) gestational age at delivery. Severe morbidity was defined as bronchopulmonary dysplasia, severe germinal matrix cerebral hemorrhage grade III or IV, cystic periventricular leukomalacia of more than grade I, proven neonatal sepsis or necrotizing enterocolitis (from Lees et al. [49] and Bilardo et al. [50])

between 26 and 32 weeks of gestation, as shown in the flowchart of the recommended protocol (Fig. 26.3) [50], the TRUFFLE study provided other important information with implications for practice. The study clearly demonstrated that when a specific protocol is uniformly applied and pregnancies are managed by expert multidisciplinary obstetric and neonatal teams, then the outcomes are better than might be expected from contemporary data. Nearly three-quarters of women developed hypertensive disorders in pregnancy, implying the need for strict blood pressure monitoring in these women. The onset of maternal hypertension had an impact on the interval from inclusion to delivery, much shorter in women who had pre-eclampsia at inclusion (median 4 days, interquartile range (IQR) 2–10) than in those that did not (median 12 days, IQR 5–20) [48]. Finally, data presented in Fig. 26.2 might be helpful in counseling parents regarding morbidity, mortality, and adverse long-term outcomes at diagnosis and at delivery according to gestational age.

It is important to highlight that outcomes similar to that of the TRUFFLE trial can be replicated only in fetal growth restriction from 26 to 32 weeks, using the monitoring strategy and delivery decision-making based on ductus venosus Doppler in conjunction with the assessment of short-term variation obtained by computerized cardiotocography.

26.4 Trials of Middle Cerebral Artery Doppler or its Ratio to the Umbilical Artery in High-Risk Pregnancies

26.4.1 Evidence from Randomized Studies

The fetal response to hypoxemia is the redistribution of the blood flow to vital organs such as the brain, heart, and adrenal glands [5]. Thus, the so-called brain-sparing effect, or cerebral redistribution, represents a fetal adaptation to reduced

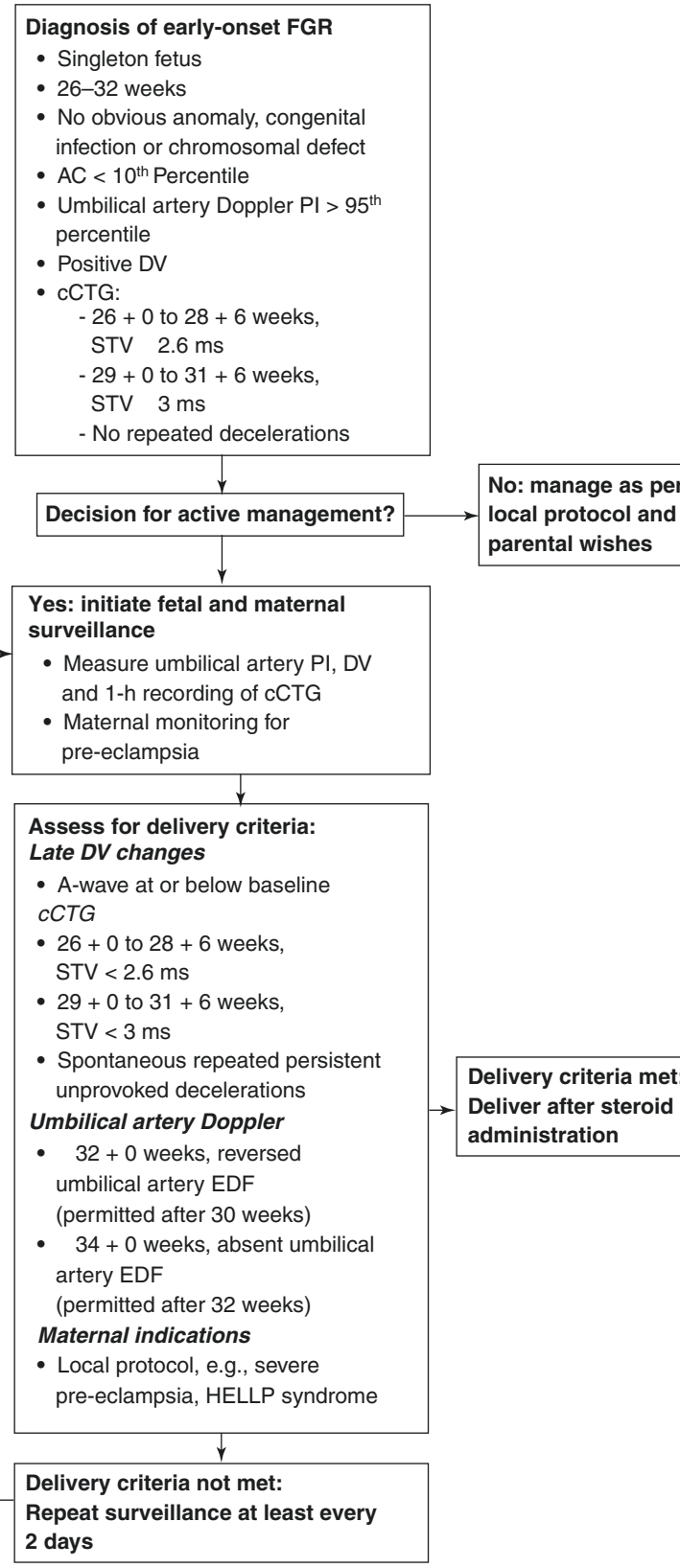

Fig. 26.3 Flowchart of the TRUFFLE protocol (from Bilardo et al. [50])

oxygen availability. This observation might be relevant especially in late fetal growth restriction where alterations of the umbilical artery and ductus venosus districts are rare and fail to identify the majority of late fetal growth-restricted fetuses [51].

Several studies have found an association between cerebral redistribution with a poorer perinatal outcome, including stillbirth [52], a higher risk of cesarean delivery [53–55], and an increased risk of abnormal neurodevelopment at birth [56] and at 2 years of age [57]. These data are also supported by systematic reviews [58–60] and meta-analyses [61, 62].

To our knowledge, the only randomized study that evaluated the impact of cerebral redistribution on a perinatal outcome in patients at high risk was the study by Ott et al [23] In this study, the addition of the middle cerebral to umbilical artery systolic/diastolic velocity waveform ratio to the modified biophysical profile was evaluated. The study included a heterogeneous group of pregnancies considered to be at a higher risk (risk of uteroplacental insufficiency, post-dates, maternal diabetes, fluid abnormalities, and others). Overall, there were no statistically significant differences in the perinatal outcome. However, when only a subgroup of fetuses at a risk of uteroplacental insufficiency was considered, a significant difference in the cesarean section rate for fetal distress was observed, with fewer cesarean sections in the intervention group (1/63, 1.6%) than in the control group (6/56, 10.7%, $p = 0.04$) [23].

There are no randomized controlled trials on the application of middle cerebral artery Doppler and its impact on long-term outcomes in high-risk pregnancies, including fetal growth restriction. This makes the quality of the evidence, on which the application of middle cerebral artery Doppler is based, extremely low, mainly based on retrospective or prospective observational data or secondary analysis of primary studies. Thus, the application of middle cerebral artery Doppler and its ratio in high-risk pregnancies, particularly in fetal growth restriction, based on high-quality studies and strong evidence is still missing, leaving it as an unresolved question. The difficulty in interpreting these studies pertains to whether abnormal cerebral Doppler is in itself injurious to fetal outcome and neurodevelopment or whether it is simply a marker of hypoxia and it is hypoxia itself that is damaging or alternatively that these Doppler changes lead to iatrogenic delivery and prematurity.

26.4.2 Implication for Practice

There is no international consensus as to the timing of delivery in late fetal growth restriction (somewhat arbitrarily defined as after 32 weeks) due to the lack of interventional management randomized trials based on Doppler indices or other biophysical tools. In fact, the national guidelines for the management of late fetal growth restriction are highly variable [63], and, hence, management is mainly based on expert opinion [64, 65].

The secondary analysis of the TRUFFLE study showed a weak association between the low middle cerebral artery pulsatility index and adverse short-term neonatal outcome and between the low middle cerebral artery pulsatility index and high umbilical-cerebral (but not cerebral-placental) ratio with 2-year adverse neurodevelopmental outcome [66]. However, the gestational age at delivery and birth weight had the most pronounced impact on these outcomes (Fig. 26.4). These data suggest that middle cerebral artery Doppler might be used to guide monitoring before 32 weeks of gestation, but there is no evidence that it should be used to determine delivery timing [67].

A recent secondary analysis of the PORTO study (Perinatal Ireland Multicenter Observational Prospective Observational Trial to Optimize Pediatric Health in Fetal Growth Restriction) has shown that fetuses with growth restriction across all gestational age epochs and with an abnormal cerebro-placental ratio (<1) had a significantly poorer neurological outcome at 3 years [68]. The authors conclude that the study "further substantiates the benefit of routine assessment of cerebroplacental ratio in fetal growth restricted pregnancies and for counseling parents regarding the long-term outcome of affected infants." When

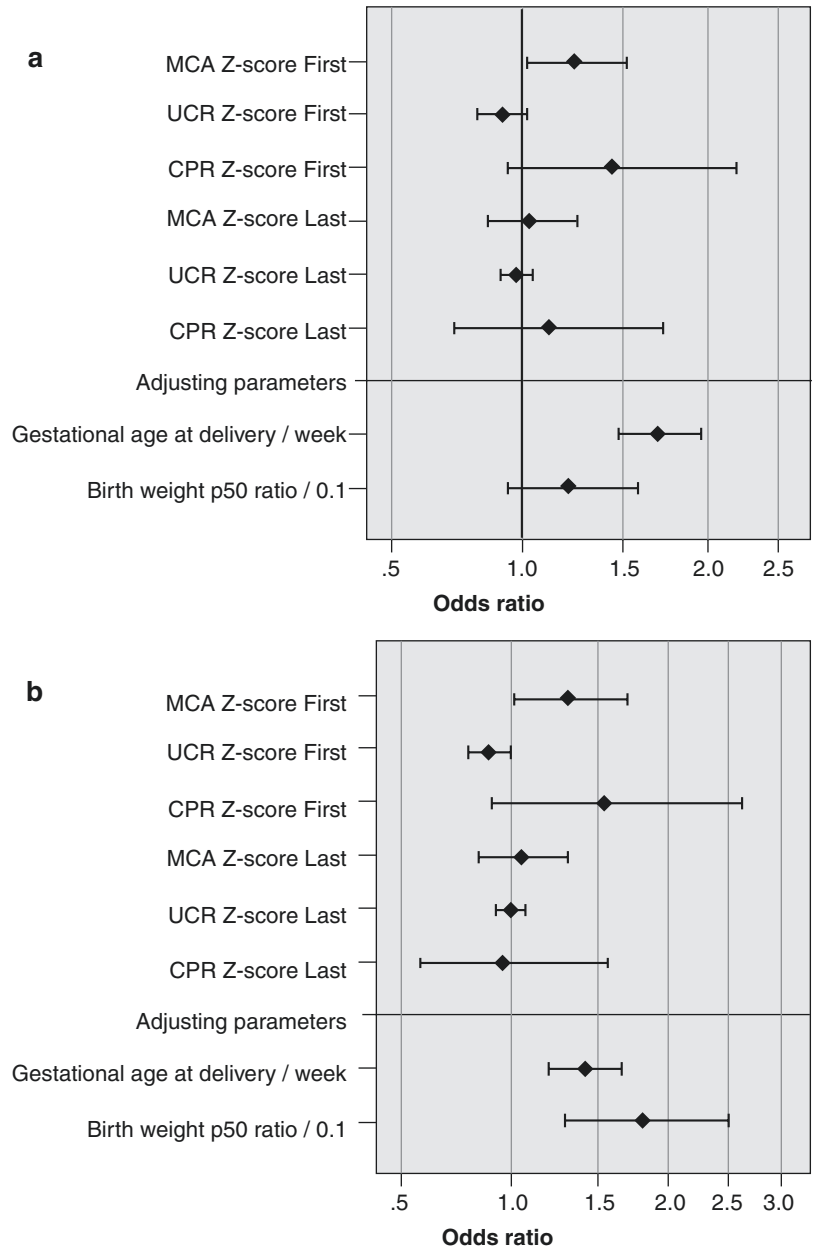

Fig. 26.4 Secondary analysis of the TRUFFLE study: odds ratios with 95% confidence intervals for neonatal and 2-year infant outcome (from Stampalija et al. [66]). The upper panel (**a**) represents the odds ratios for neonatal outcome (survival until the first discharge home without severe morbidity), and the lower panel (**b**) represents the odds ratios for the 2-year infant outcome (survival without neurological impairment at 2 years) of the *z*-scores of the middle cerebral artery (MCA) pulsatility index, umbilical-cerebral ratio (UCR), and cerebroplacental ratio (CPR) at inclusion (first) and within 1 week before delivery (last), adjusted for birth weight, p50 ratio, and gestational age. The odds ratios of the adjusting parameters are shown below the horizontal line. DV p95: early changes in the ductus venosus (DV-PI>95th percentile); DV no A: late changes in the ductus venosus (no or reverse A-wave flow)

assessing an adverse short- or long-term outcome, both the severity of growth restriction and gestational age at delivery should be taken into account while representing an independent risk factor for the adverse outcome. It still remains to be elucidated whether cerebral redistribution is an independent risk factor for an adverse outcome or it "only" reflects the severity of growth restriction.

The TRUFFLE-2 feasibility study explored the association between cerebral redistribution and outcome in late preterm (32^{+0}–36^{+6} weeks of gestation) pregnancies at a risk of fetal growth restriction [69]. In this large multi-center (33 European centers) prospective cohort study of 862 women, infants with composite adverse outcome were delivered at a lower gestational age (36 versus 38 weeks) with a lower birth weight (1900 g ver-

sus 2540 g). However, the first observation of cerebral redistribution after inclusion, defined as the middle cerebral artery pulsatility index below the fifth centile and specific umbilicoplacental ratio *z*-score thresholds (1.5 at 32–33 weeks and 1.0 at 34–36 weeks, respectively), had the highest relative risk of a composite adverse outcome (RR 2.1; 95% CI 1.5–3.2 and RR 2.1; 95% CI 1.4–3.1, respectively). This effect was independent of gestational age below 36 weeks of gestation, as shown in Tables 26.3 and 26.4. These data would support an association between cerebral redistribution and adverse outcome, but like other un-blinded observational studies, the weakness is that there might be a treatment paradox. Finally, the association does not imply causality. Thus, a randomized trial is required to answer the uncertainties regarding delivery timing in late fetal growth restriction in relation to cerebral blood flow redistribution.

26.5 Implications for Research

The type and frequency of monitoring after the identification of abnormal umbilical artery Doppler in fetal growth restriction is still not clear, or, at least, it has not been tested by randomized controlled trials. There is no doubt that umbilical artery assessment is of crucial importance to identify fetal growth restriction, especially early-onset, due to placental insufficiency. However, the best delivery timing and impact on short- and long-term outcomes, in the presence of absent or reverse end-diastolic flow or increased pulsatility index in the umbilical artery, from 32 weeks, has not been appropriately evaluated in randomized controlled trials.

Despite emerging awareness that there might be an association between cerebral blood flow redistribution and adverse perinatal outcome, in the absence of randomized controlled trials, it is still not clear whether the assessment and delivery decision based on Doppler evaluation of cerebral blood flow redistribution is beneficial in terms of short- and long-term neurodevelopmental outcomes and which is the optimal gestational age to deliver (beside the optimal Doppler parameter and threshold).

Key Messages

The available evidence from randomized controlled trials suggests:

- Umbilical artery assessment improves perinatal outcome in high-risk pregnancies, particularly in pregnancies at risk of placental insufficiency.
- In early fetal growth restriction (26–32 weeks), the best outcome at 2 years is obtained by timing the decision for delivery on combined monitoring by the ductus venosus and short-term variation obtained by computerized cardiotocography.
- In late fetal growth restriction (after 32 weeks), there is little or no evidence to inform the frequency of Doppler evaluation and the timing of delivery based on umbilical artery and/or middle cerebral artery assessment.

Table 26.3 Composite adverse outcome and gestational age at delivery for fetuses with signs of cerebral blood flow redistribution compared to those that always had a normal fetal Doppler, specified for gestational age at the ultrasound Doppler examination. Women who had an abnormal ultrasound were only counted once at the gestational age epoch when the first abnormal Doppler was registered. Women with normal Doppler could have ultrasound at more than one gestational age epoch after inclusion. Totals are therefore higher than the total number of included women. Middle cerebral artery pulsatility index cut-off at the fifth percentile

	Below cut-off at least once		Always above cut-off		RR (95% CI) for composite adverse outcome	
Gestational epoch at Doppler	Composite adverse outcome	Gestational age at delivery	Composite adverse outcome	Gestational age at delivery		*p*
32–33 weeks	24/63 = 38%[a]	36 (34–38)[a]	26/283 = 9%	38 (37–39)	4.1 (2.6–6.7)	<0.01
34–35 weeks	14/94 = 15%[a]	37 (36–38)[a]	37/513 = 7%	38 (37–40)	2.1 (1.2–3.4)	0.01
36 weeks	6/63 = 10%	38 (37–38)[a]	27/568 = 5%	39 (38–40)	2.0 (0.8–4.7)	0.1

[a] Statistically significant difference from fetuses that always had a middle cerebral artery pulsatility index below cut-off (a chi-square test or the Mann–Whitney test)

Table 26.4 Composite adverse outcome and gestational age at delivery for fetuses with signs of cerebral blood flow redistribution compared to those that always had a normal fetal Doppler, specified for gestational age at the ultrasound Doppler examination. Women who had an abnormal ultrasound were only counted once at the gestational age epoch when the first abnormal Doppler was registered. Women with normal Doppler could have ultrasound at more than one gestational age epoch after inclusion. Totals are therefore higher than the total number of included women. Umbilicocerebral ratio gestational age-specific cut-off at a *z*-score of 1.5 at 32–33 weeks and 1.0 at 34–36 weeks

	Above cut-off at least once		Always below cut-off		RR (95% CI) for composite adverse outcome	
Gestational epoch at Doppler	Composite adverse outcome	Gestational age at delivery	Composite adverse outcome	Gestational age at delivery		*p*
32–33 weeks	12/31 = 39%[a]	34 (3–36)[a]	33/291 = 11%	38 (37–39)	3.4 (2.0–5.9)	<0.01
34–35 weeks	15/86 = 17%[a]	36 (35–37)[a]	46/563 = 8%	38 (37–40)	2.1 (1.2–3.7)	0.01
36 weeks	3/45 = 8%	37 (37–38)[a]	34/626 = 5%	39 (38–40)	1.2 (0.4–3.8)	0.7

[a] Statistically significant difference from fetuses that always had an umbilicocerebral ratio below cut-off (a chi-square test or the Mann–Whitney test)

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