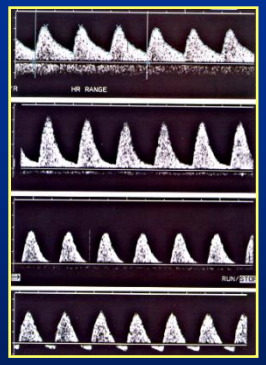
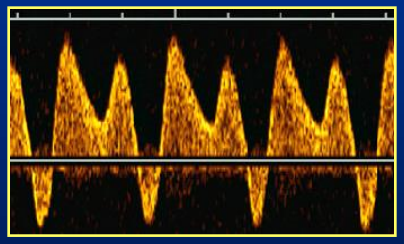
Early Fetal Growth Restriction TRUFFLE study

K. Hecher
University Medical Center Hamburg-Eppendorf
Hamburg, Germany

on behalf of the TRUFFLE Group

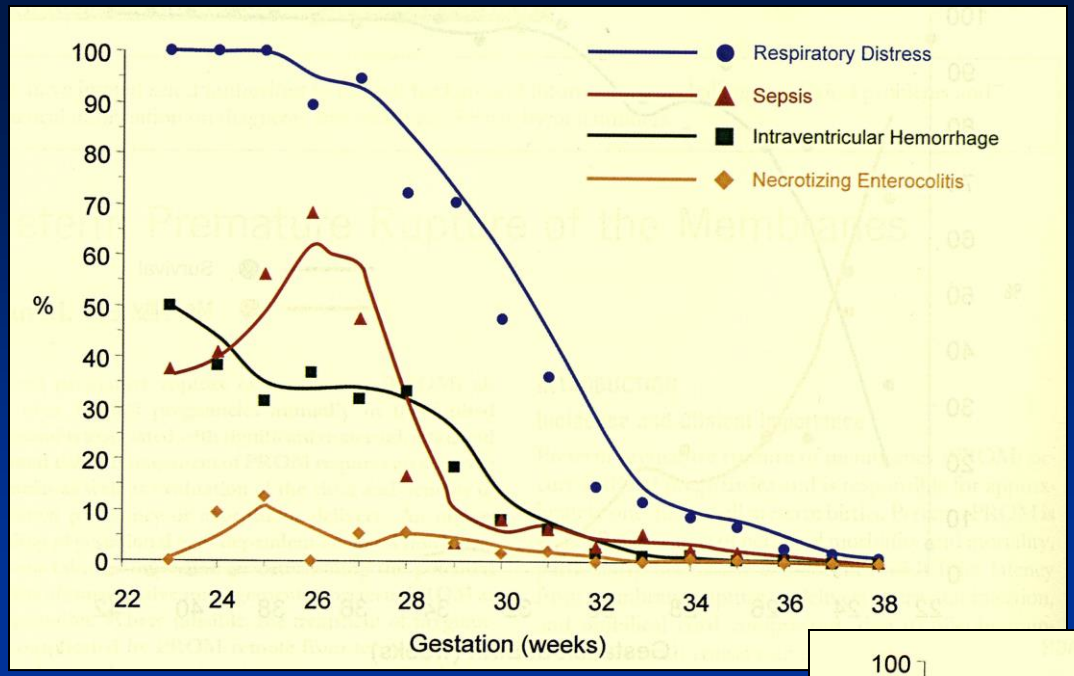


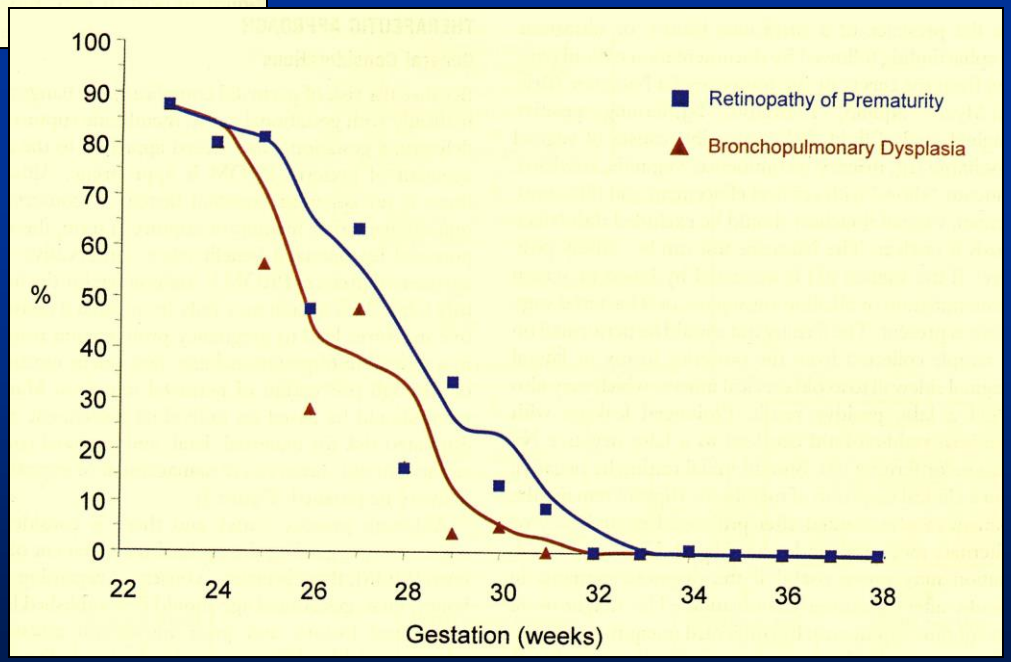


Timing of Delivery

‘I am a fetus in the womb.
I fear it may become my tomb.
If only I could give a shout
To make my doctor get me out!’

unknown medical student, Dublin; Br J Obstet Gynaecol

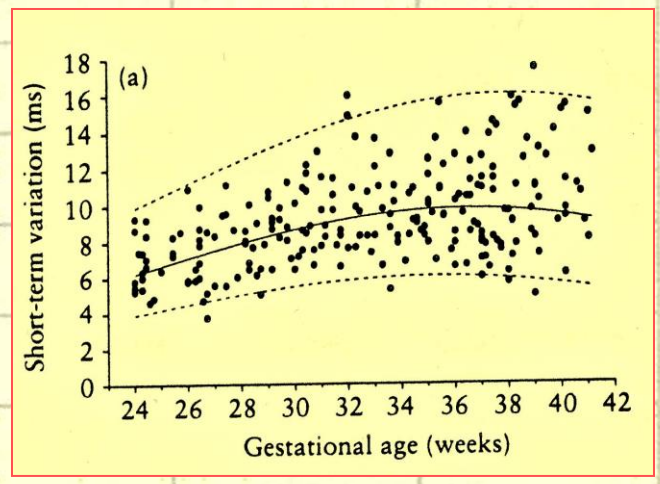




Mercer, Treatment of Preterm PROM Obstet Gynecol 2003

Short Term Variation

longitudinal monitoring



milliseconds

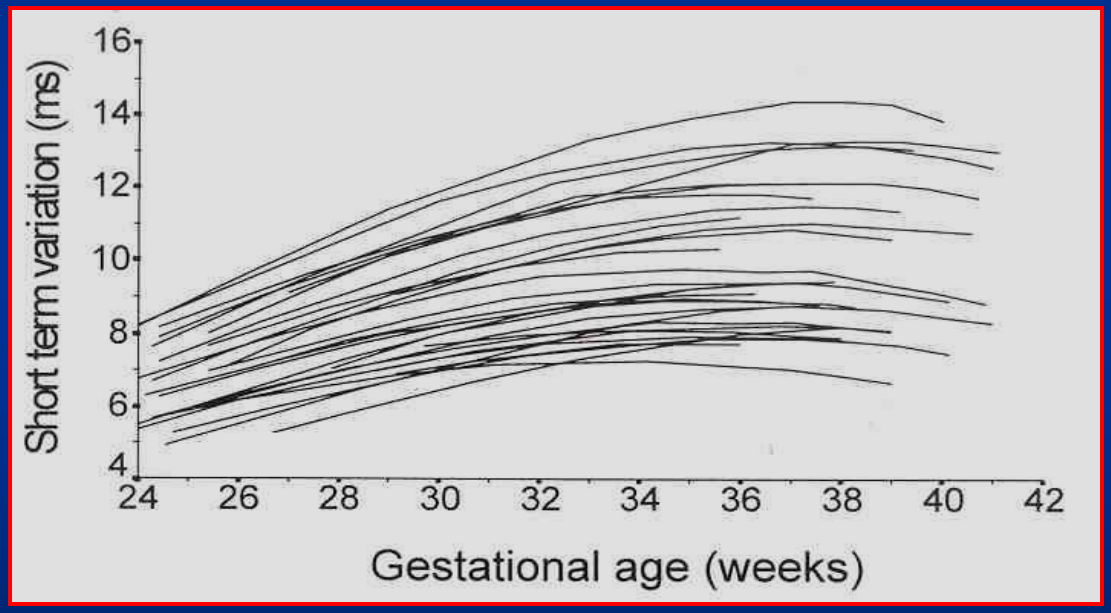
0
1
2
3
4
5
6
7
8
9
10

31/10
01/11
02/11
03/11
04/11
05/11

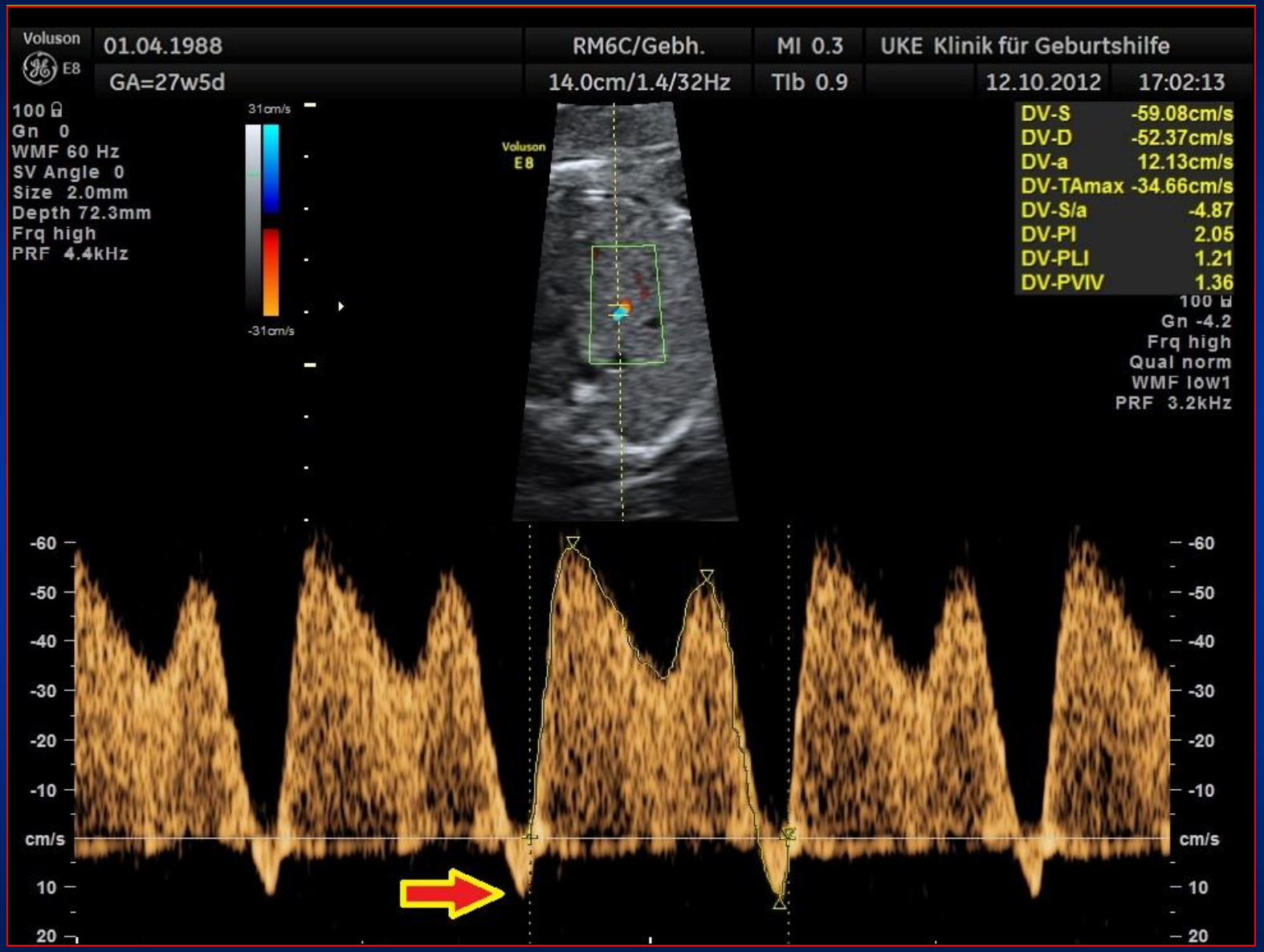
visit date

Antenatal CTG

Use each fetus as its own control



(Ilse Nijhuis et al, 1998)


Voluson
E8
01.04.1988
GA=27w5d
RM6C/Gebh.
14.0cm/1.4/32Hz
MI 0.3
TIb 0.9
UKE Klinik für Geburtshilfe
12.10.2012
17:02:13
100
Gn 0
WMF 60 Hz
SV Angle 0
Size 2.0mm
Depth 72.3mm
Frq high
PRF 4.4kHz
31cm/s
-31cm/s
DV-S -59.08cm/s
DV-D -52.37cm/s
DV-a 12.13cm/s
DV-TAmax -34.66cm/s
DV-S/a -4.87
DV-PI 2.05
DV-PLI 1.21
DV-PVIV 1.36
100
Gn -4.2
Frq high
Qual norm
WMF low1
PRF 3.2kHz
-60
-50
-40
-30
-20
-10
cm/s
10
20

Longitudinal Doppler Study

Hamburg, **A**msterdam, **U**trecht and **L**ondon

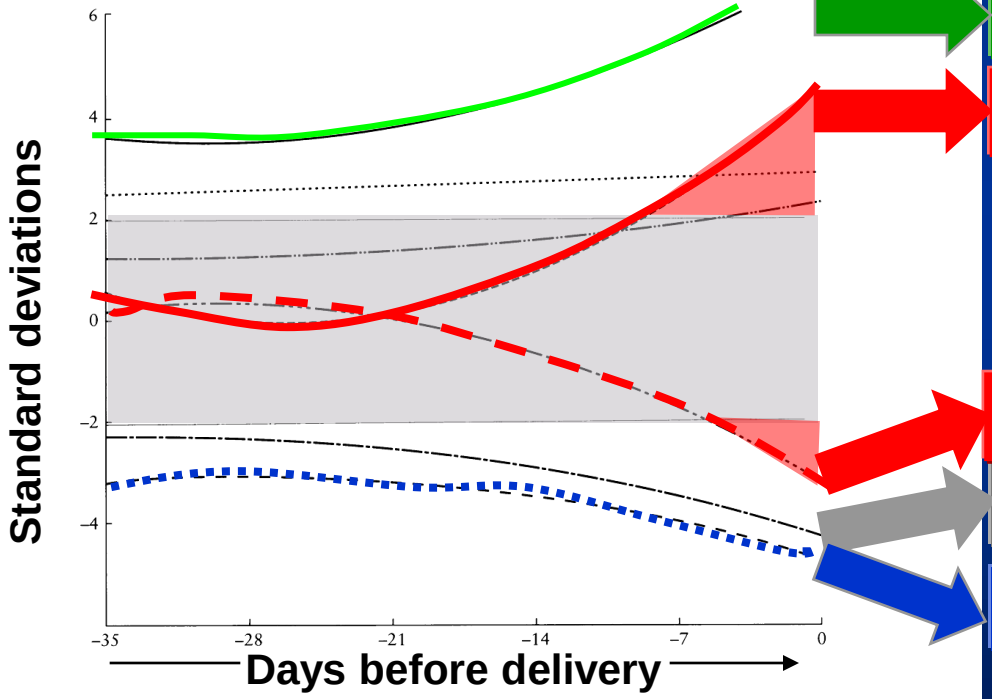


Figure 3 Trends over time of variables in relation to time before delivery and reference ranges (±2 SD) for Group 1 (fetuses delivered before or at 32 weeks of gestation). ——, umbilical artery; – – –, ductus venosus; ·····, aorta; —·—, inferior vena cava; —·—·—, short-term variation; —·—, middle cerebral artery; – –, amniotic fluid index.

Umbilical artery PI

Ductus venosus PI

STV

Middle Cerebral artery

Amniotic Fluid Index

Hecher et al. Ultrasound Obstet Gynecol 2001

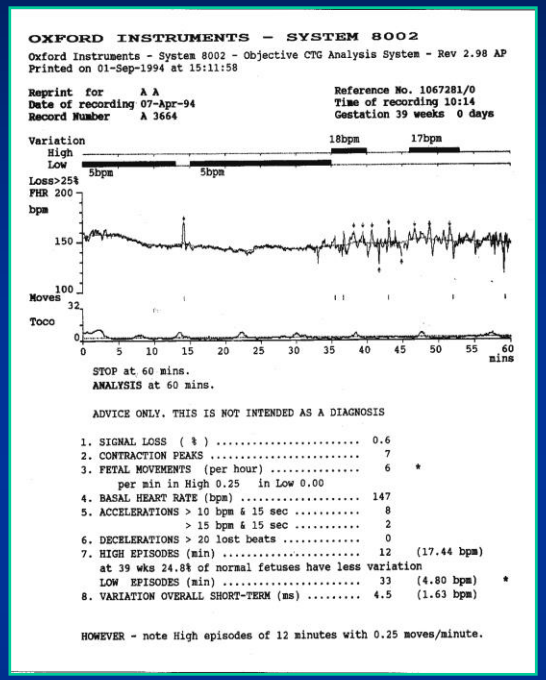
TRUFFLE

Randomized Management Study in IUGR

- **Computerized CTG**
- **Early ductus venosus**
- **Late ductus venosus**

For all as safety net: computerized CTG, umbilical artery Doppler

TRUFFLE



OXFORD INSTRUMENTS – SYSTEM 8002

Oxford Instruments - System 8002 - Objective CTG Analysis System - Rev 2.98 AP
Printed on 01-Sep-1994 at 15:11:58

Reprint for A A
Date of recording 07-Apr-94
Record Number A 3664

Reference No. 1067281/0
Time of recording 10:14
Gestation 39 weeks 0 days

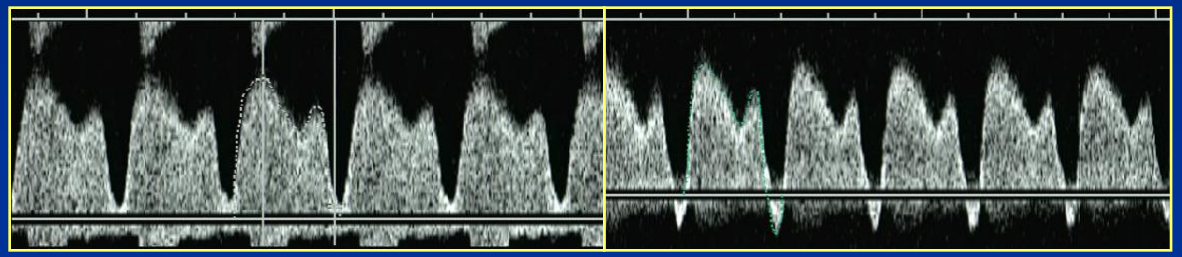
Variation
High
Low
18bpm 17bpm
5bpm 5bpm
Loss>25%
FHR 200
bpm
150
100
Moves
32
Toco
0
0 5 10 15 20 25 30 35 40 45 50 55 60
mins

STOP at 60 mins.
ANALYSIS at 60 mins.

ADVICE ONLY. THIS IS NOT INTENDED AS A DIAGNOSIS

1. SIGNAL LOSS (%)	0.6	
2. CONTRACTION PEAKS	7	
3. FETAL MOVEMENTS (per hour)	6	*
per min in High 0.25 in Low 0.00		
4. BASAL HEART RATE (bpm)	147	
5. ACCELERATIONS > 10 bpm & 15 sec	8	
> 15 bpm & 15 sec	2	
6. DECELERATIONS > 20 lost beats	0	
7. HIGH EPISODES (min)	12	(17.44 bpm)
at 39 wks 24.8% of normal fetuses have less variation		
LOW EPISODES (min)	33	(4.80 bpm) *
8. VARIATION OVERALL SHORT-TERM (ms)	4.5	(1.63 bpm)

HOWEVER - note High episodes of 12 minutes with 0.25 moves/minute.



A B

CTG: STV < 3.5 (26-29w)
STV < 4 (29-32w)

Early DV: PIV>95th P.

Late DV: zero/rev. ‘a‘

For all as safety net: STV < 2.6/<3; UA: AEDF >34w, reverse flow >32w

TRUFFLE Group 2005

2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial

*Christoph C Lees, Neil Marlow, Aleid van Wassenaer-Leemhuis, Birgit Arabin, Caterina M Bilardo, Christoph Brezinka, Sandra Calvert, Jan B Derks, Anke Diemert, Johannes J Duvekot, Enrico Ferrazzi, Tiziana Frusca, Wessel Ganzevoort, Kurt Hecher, Pasquale Martinelli, Eva Ostermayer, Aris T Papageorghiou, Dietmar Schlembach, K T M Schneider, Baskaran Thilaganathan, Tullia Todros, Adriana Valcamonico, Gerard H A Visser, Hans Wolf, for the TRUFFLE study group**

Lancet 2015;385:2162-72

n=503

Any hypertensive maternal morbidity	**72%**
Delivery indication < 32 weeks	**71%**
Birth weight (g)	**1020 (±320)**
GA at delivery (completed weeks + days)	**30 + 5 (±16)**

TRUFFLE outcome at 2yrs

Study group at inclusion	**503**
Infants with known outcome	**443(88%)**
Survivors evaluated for primary outcome (% of survivors at 2 yrs, n=463)	**402 (87%)**
Survival without impairment **Percentage of evaluated surviving infants** **Percentage of all infants with known outcome**	**363** **90% (363/402)** **82% (363/443)**
Components of abnormal outcome	
Perinatal/Infant death to 2 years	41 (8%)
Impairments at 2 years	39 (10%)
Cerebral palsy (GMFCS >1)	6 (1%)
Neurosensory impairment	5 (1%)
DQ≤85	26 (6%)
No test result, but reported impaired	11 (3%)

TRUFFLE outcome at 2yrs

	CTG STV	DV p95	DV no A		Total
Survival without impairment % of evaluated surviving infants (n=402)	111/131 85%	119/131 91%	133/140 95%		363/402 90%

P<0.005

	CTG STV	DV p95	DV no A		Total
Survival without impairment % of all infants with known outcome (n=443)	111/144 77%	119/142 84%	133/157 85%		363/443 82%
Components of abnormal outcome					
Perinatal/Infant death to 2 years	13 (8%)	11 (7%)	17 (10%)		41 (8%)
Impairments at 2 years	20 (15%)	12 (9%)	7 (5%)		39 (10%)

P=0.09

Perinatal death (n.s.)

Neurodisability

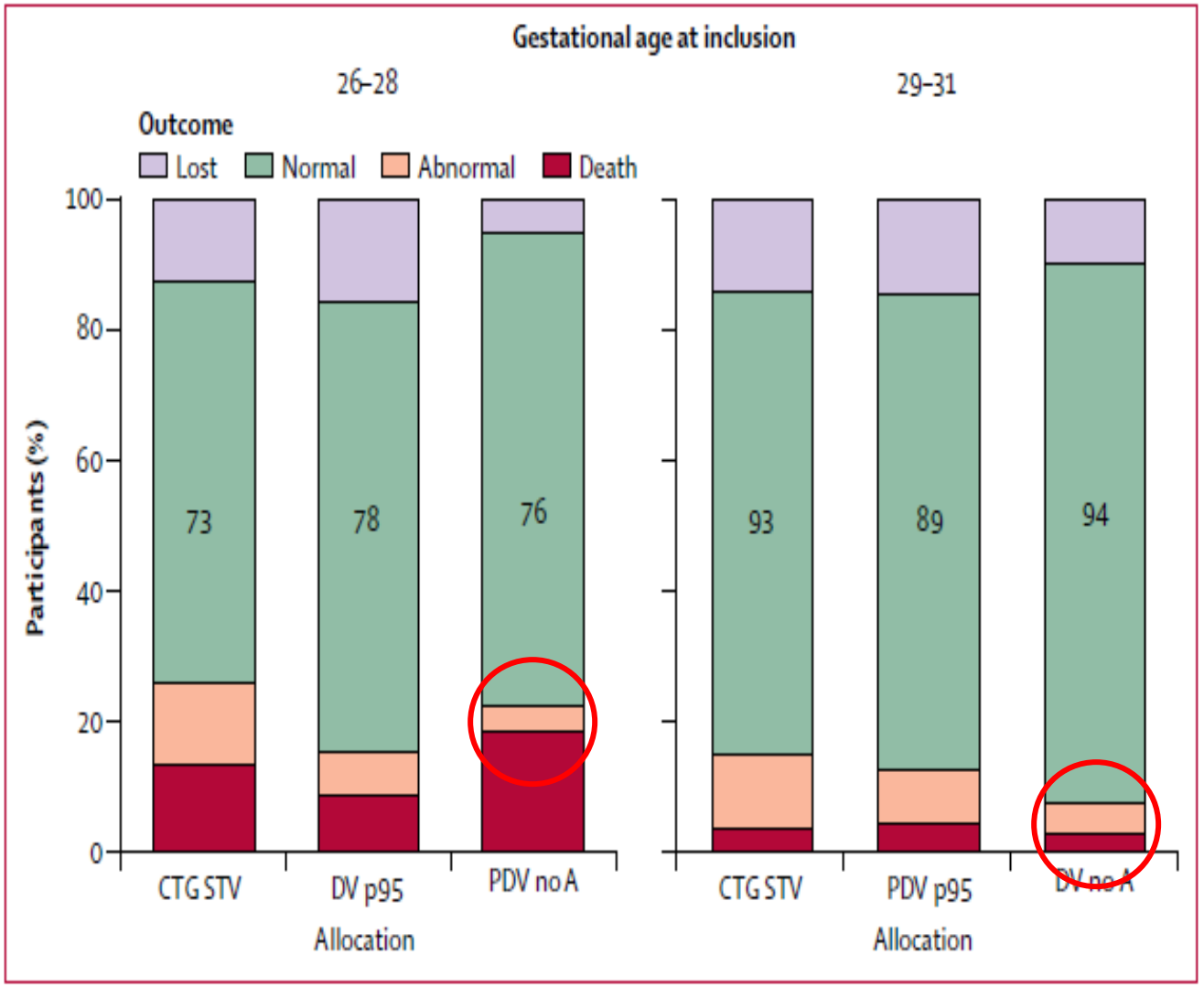


Figure 2: Outcome for all cases

OBSTETRICS

Is middle cerebral artery Doppler related to neonatal and 2-year infant outcome in early fetal growth restriction?

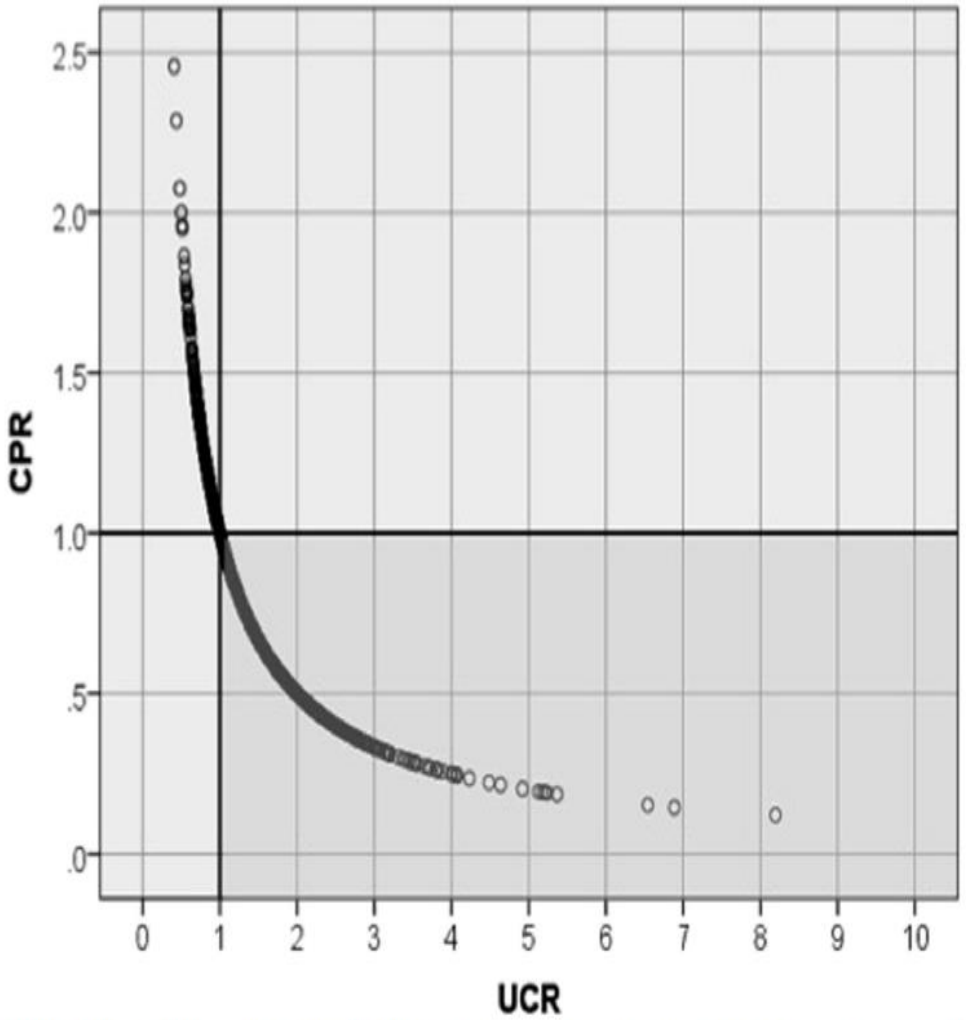
Tamara Stampalija, MD; Birgit Arabin, MD; Hans Wolf, MD; Caterina M. Bilardo, MD; Christoph Lees, MD; on behalf of the TRUFFLE investigators

Cite this article as: Stampalija T, Arabin B, Wolf H, et al. 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.

CONCLUSION: In a monitoring protocol based on ductus venosus and cardiotocography in early fetal growth restriction (26^{+0}–31^{+6} weeks of gestation), the impact of middle cerebral artery Doppler and its ratios on outcome is modest and less marked than birthweight and delivery gestation. It is unlikely that middle cerebral artery Doppler and its ratios are informative in optimizing the timing of delivery in fetal growth restriction before 32 weeks of gestation. The umbilicocerebral ratio allows for a better differentiation in the abnormal range than the cerebroplacental ratio.

FIGURE 3

UCR vs CPR at study inclusion



UCR vs CPR at study inclusion in the TRUFFLE study (n = 374). The *shaded area* defines an abnormal test with a cutoff at 1.0.

CPR, cerebroplacental ratio; *TRUFFLE*, Trial of Randomized Umbilical and Fetal Flow in Europe; *UCR*, umbilicocerebral ratio.

Stampalija et al. Middle cerebral artery Doppler in early fetal growth restriction. Am J Obstet Gynecol 2017.

TRUFFLE group findings & implications for management:

<32 weeks, management based on ductus venosus:

lower risk of neuro-impairment if delivery is based on absent or reversed 'a' wave

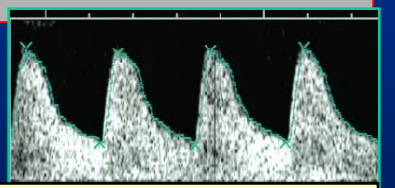
OR if CTG STV severely abnormal

BUT there may be a slightly higher risk of perinatal death

After 30 weeks: umbilical artery Doppler, deliver if…

- at 30-32 wks reversed EDF
- at 32-34 wks absent EDF
- at 34-36 wks increased PI (>95th centile)

U/C ratio??



- ***However, there was no DV safety net for the CTG***
- ***Always use both, cCTG and DV Doppler!***
- ***Don't wait until both are severely abnormal***

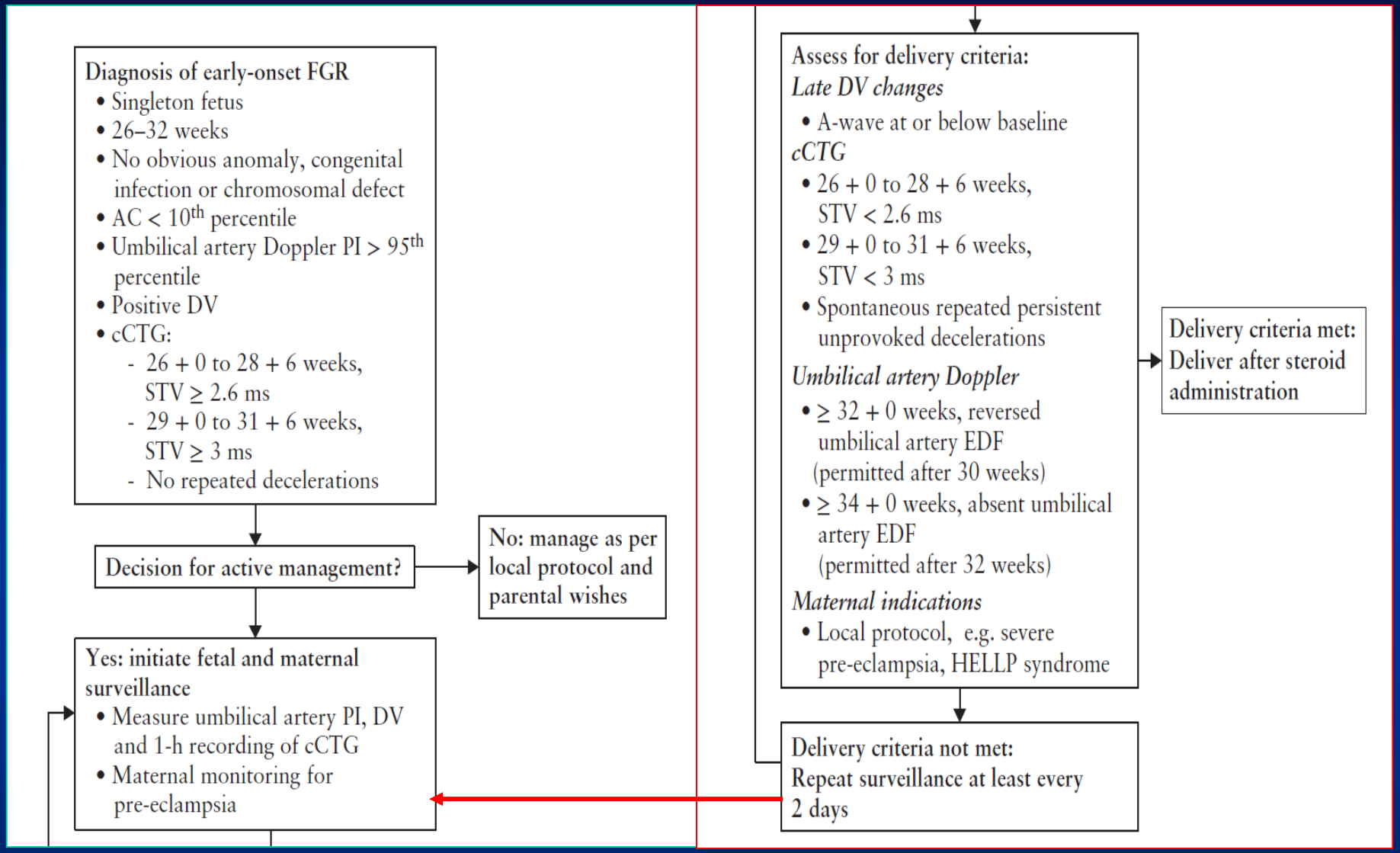
TRUFFLE 2

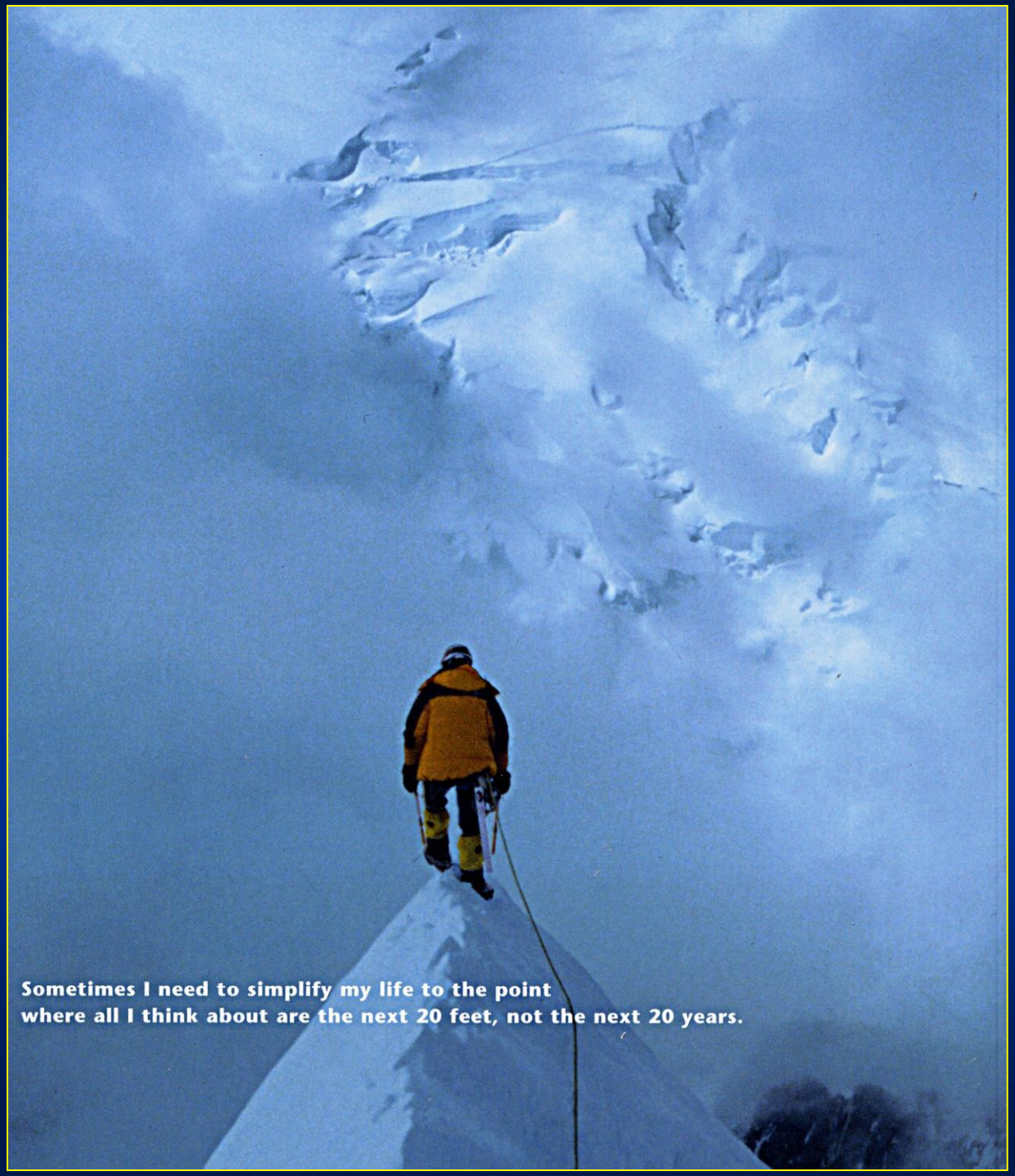
Ultrasound Obstet Gynecol 2017; 50: 285–290
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.18815

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[#]


Diagnosis of early-onset FGR
• Singleton fetus
• 26–32 weeks
• No obvious anomaly, congenital infection or chromosomal defect
• AC < 10th percentile
• Umbilical artery Doppler PI > 95th percentile
• Positive DV
• cCTG:
- 26 + 0 to 28 + 6 weeks, STV ≥ 2.6 ms
- 29 + 0 to 31 + 6 weeks, STV ≥ 3 ms
- No repeated decelerations
Decision for active management?
No: manage as per local protocol and parental wishes
Yes: initiate fetal and maternal surveillance
• Measure umbilical artery PI, DV and 1-h recording of cCTG
• Maternal monitoring for pre-eclampsia
Assess for delivery criteria:
Late DV changes
• A-wave at or below baseline
cCTG
• 26 + 0 to 28 + 6 weeks, STV < 2.6 ms
• 29 + 0 to 31 + 6 weeks, STV < 3 ms
• Spontaneous repeated persistent unprovoked decelerations
Umbilical artery Doppler
• ≥ 32 + 0 weeks, reversed umbilical artery EDF (permitted after 30 weeks)
• ≥ 34 + 0 weeks, absent umbilical artery EDF (permitted after 32 weeks)
Maternal indications
• Local protocol, e.g. severe pre-eclampsia, HELLP syndrome
Delivery criteria met: Deliver after steroid administration
Delivery criteria not met: Repeat surveillance at least every 2 days

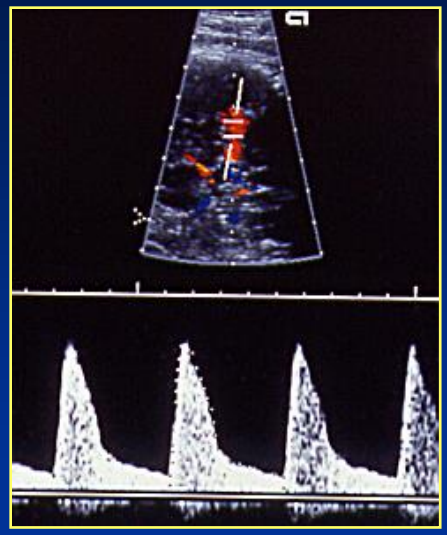

Sometimes I need to simplify my life to the point
where all I think about are the next 20 feet, not the next 20 years.

Next step…

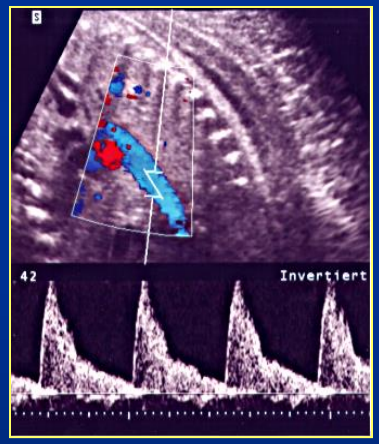
TRRIAL of
UMBILICAL *and*
FETAL
FLOW *in*
EUROPE

RCT late IUGR (>32 weeks)

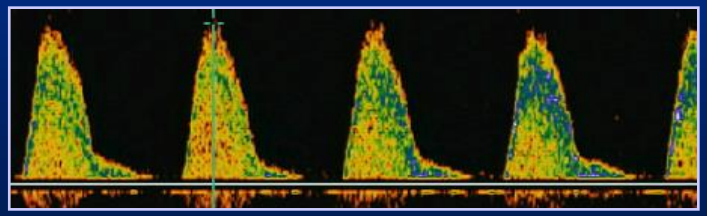
BLOOD FLOW REDISTRIBUTION

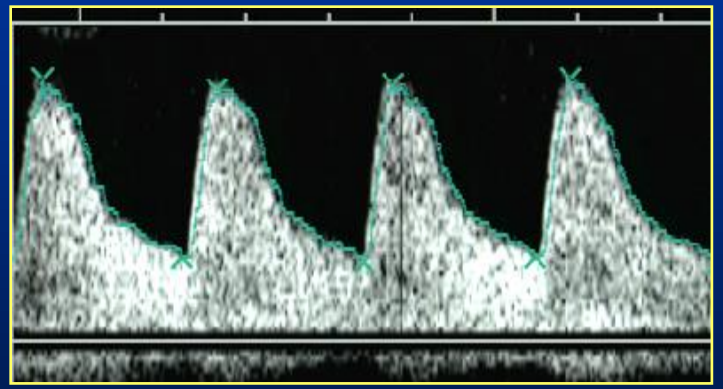


MCA



Aorta





Cerebral-Umbilical Doppler Ratio As a Predictor of Adverse Perinatal Outcome

DANDOLO GRAMELLINI, MD, MARIA CRISTINA FOLLI, MD,
STEFANO RABONI, MD, EUGENIO VADORA, MD, AND ADELCHI MERIALDI, MD

Obstet Gynecol 1992;79:416

Accuracy (%):	
MCA	79
UA	83
CUR	90

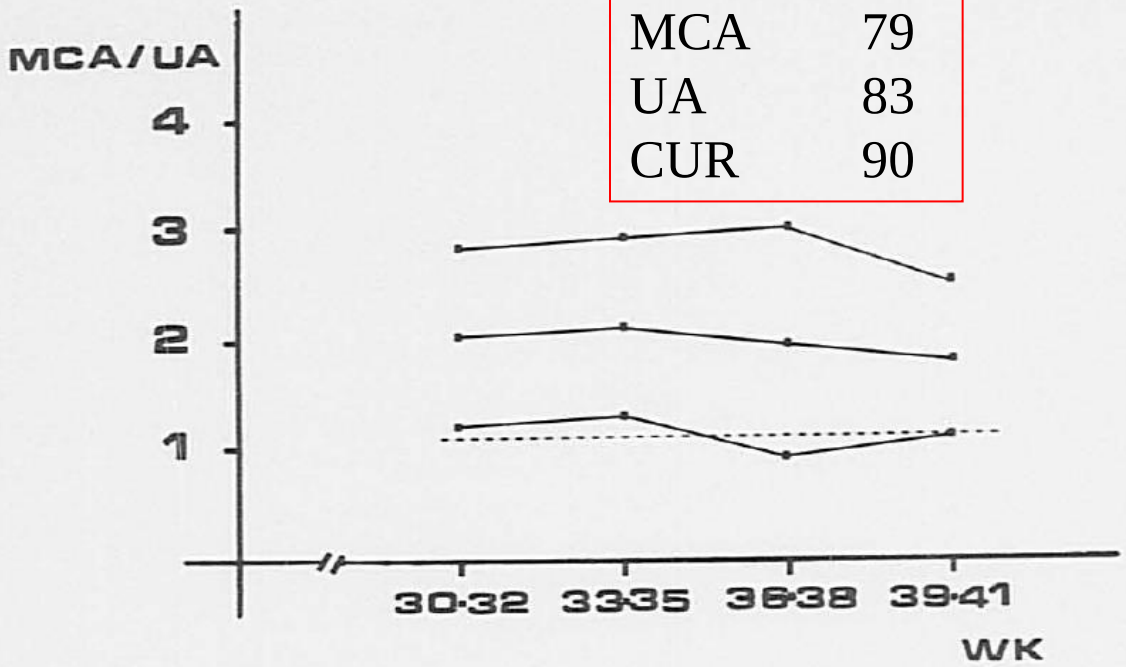


Figure 1. Cerebral-umbilical Doppler ratio in normal pregnancies. The horizontal dotted line represents the suggested cutoff value. MCA = middle cerebral artery; UA = umbilical artery.

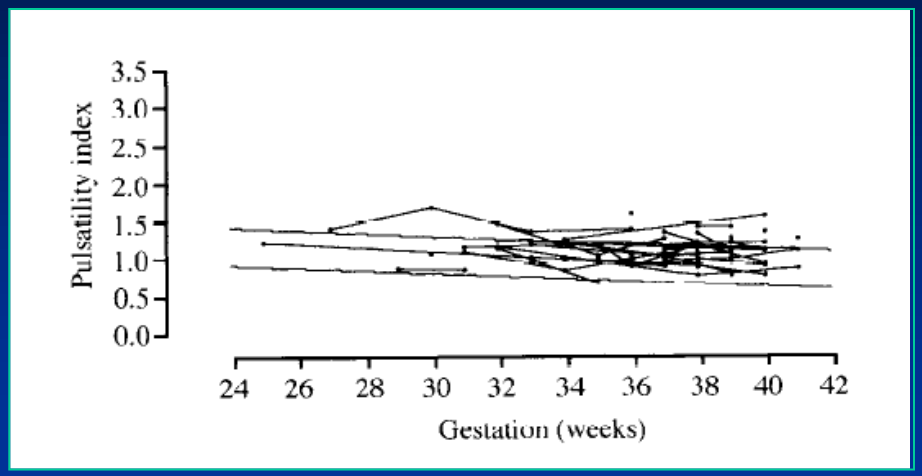
Ultrasound Obstet. Gynecol. 2 (1992) 266–271

Potential for diagnosing imminent risk to appropriate- and small-for-gestational-age fetuses by Doppler sonographic examination of umbilical and cerebral arterial blood flow

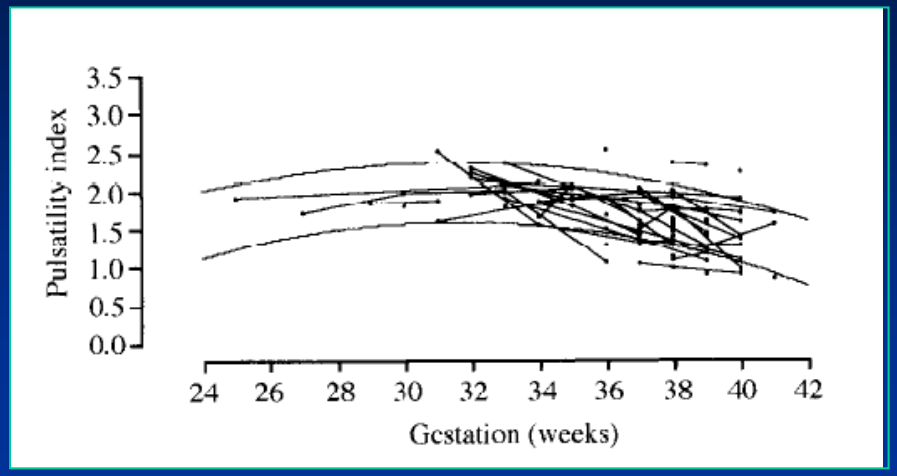
K. Hecher, R. Spernol, H. Stettner and S. Szalay*

Department of Obstetrics and Gynecology, General Hospital, Klagenfurt, and *Institute of Mathematics, University of Klagenfurt, Austria

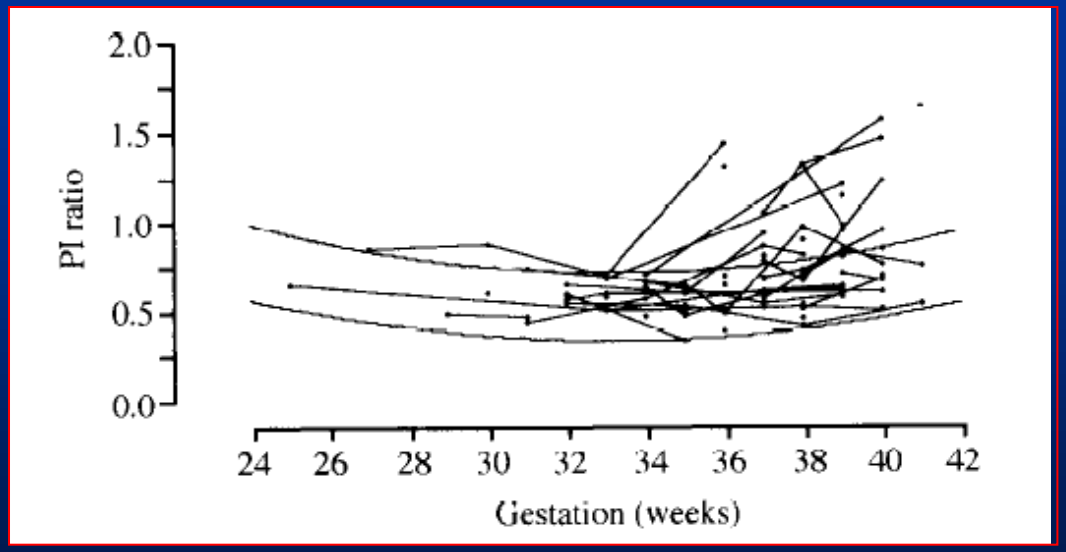
Umbilical Artery



Middle Cerebral Artery



UC-Ratio



Hecher et al. UOG 1992;2

Ultrasound Obstet Gynecol 2020; 55: 68–74
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20354.

Comparative analysis of 2-year outcomes in GRIT and TRUFFLE trials

W. GANZEVOORT[1], J. G. THORNTON[2], N. MARLOW[3], B. THILAGANATHAN[4,5], B. ARABIN[6], F. PREFUMO[7], C. LEES[8,9] and H. WOLF[1], for the GRIT Study Group* and the TRUFFLE Study Group†

CONTRIBUTION

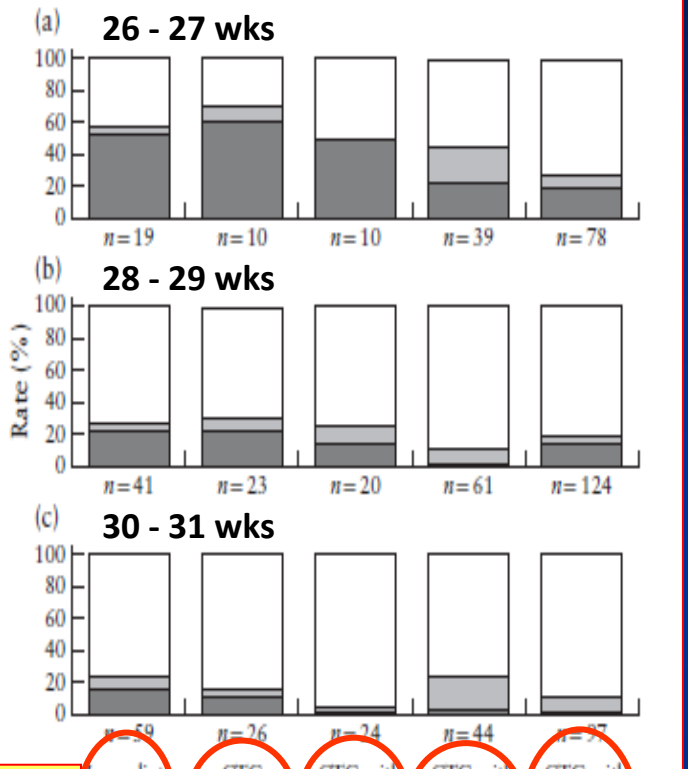
What are the novel findings of this work?

This work provides a comparative analysis of the effect on perinatal outcome of several monitoring techniques for early-onset fetal growth restriction employed in two randomized trials. The rate of survival without neurodevelopmental impairment at 2 years was highest in pregnancies monitored using computerized cardiotocography and ductus venosus Doppler.

What are the clinical implications of this work?

This analysis supports the hypothesis that the optimal method for fetal monitoring in pregnancies complicated by early-onset fetal growth restriction is a combination of computerized cardiotocography and ductus venosus Doppler assessment.

Outcomes according to GA at randomization, monitoring method (left) and year of randomization (right)



Survival % without impairment

70	69	80	77	84

Figure 1 Rates of normal development (□), neurodevelopmental impairment (■) and perinatal death (■) by 2 years of age in

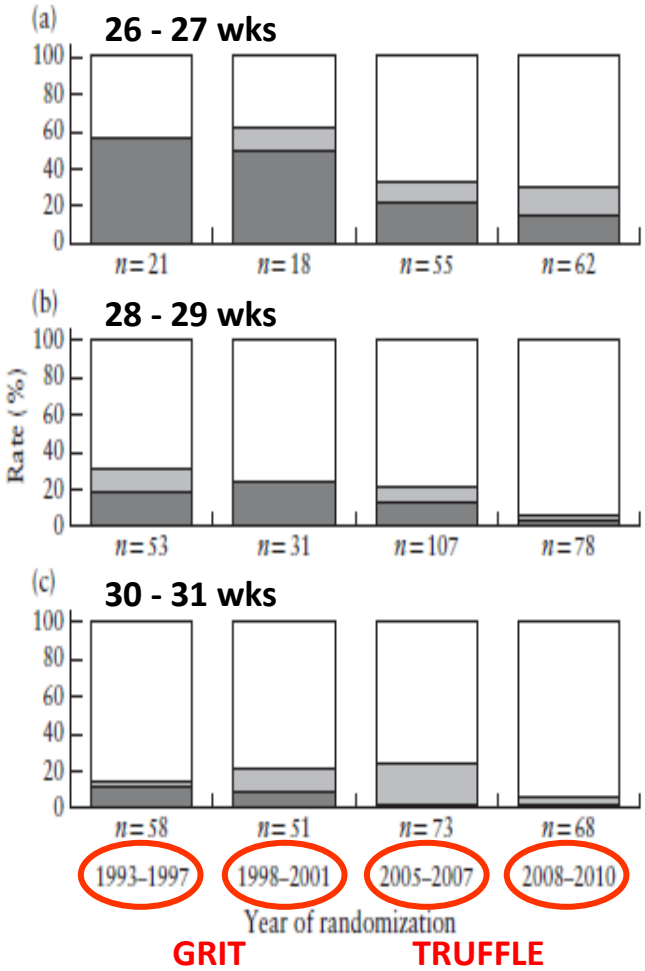


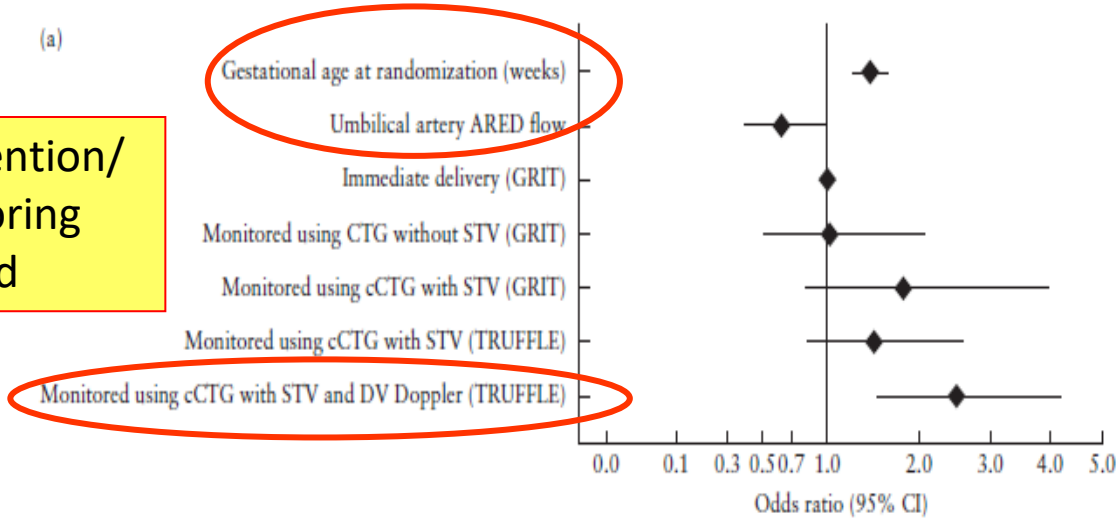
Figure 2 Rates of normal development (□), neurodevelopmental impairment (■) and perinatal death (■) by 2 years of age in children

Neonatal or late death was more frequent in GRIT (**18% vs 6%; P<0.01**)

Fetal death rate was similar (4.8% vs 5.5%)

Odds ratio for survival without neurodevelopmental impairment at 2 years)

Intervention/ monitoring method



Year of inclusion

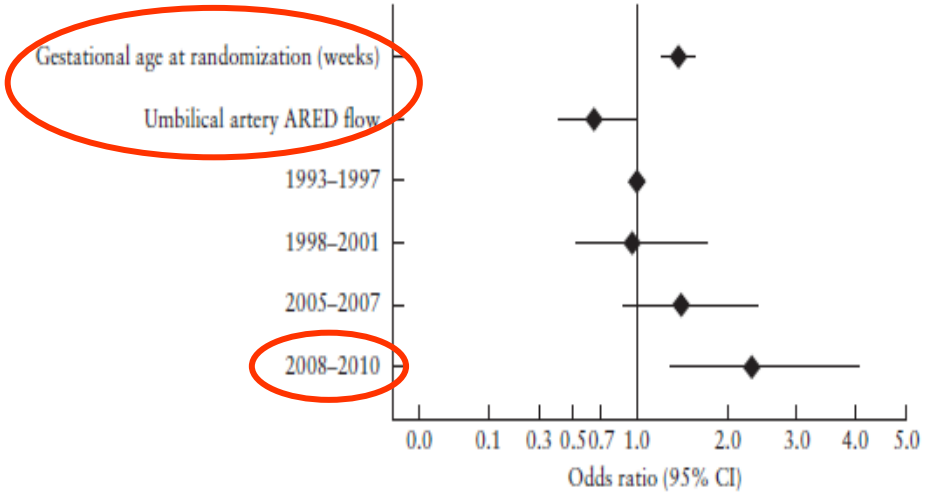


Figure 3 Odds ratios for survival without neurodevelopmental impairment at 2 years in children from pregnancies complicated by

Ultrasound Obstet Gynecol 2020; 56: 173–181
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.22125.

Fetal cerebral Doppler changes and outcome in late preterm fetal growth restriction: prospective cohort study

T. STAMPALIJA[1,2], J. THORNTON[3], N. MARLOW[4], R. NAPOLITANO[4,5], A. BHIDE[6], T. PICKLES[7], C. M. BILARDO[8,9], S. J. GORDIJN[9], W. GYSELAERS[10], H. VALENSISE[11], K. HECHER[12], R. K. SANDE[13], P. LINDGREN[14], E. BERGMAN[15], B. ARABIN[16], A. C. BREEZE[17], L. WEE[18], W. GANZEVOORT[8], J. RICHTER[19], A. BERGER[20], J. BRODSZKI[21], J. DERKS[22], F. MECACCI[23], G. M. MARUOTTI[24], K. MYKLESTAD[25], S. M. LOBMAIER[26], F. PREFUMO[27], P. KLARITSCH[28], P. CALDA[29], C. EBBING[30], T. FRUSCA[31], L. RAIO[32], G. H. A. VISSER[33], L. KROFTA[34], I. CETIN[35], E. FERRAZZI[36], E. CESARI[35], H. WOLF[8] and C. C. LEES[37], on behalf of the TRUFFLE-2 Group[#]

CONTRIBUTION

What are the novel findings of this work?

In this prospective multicenter observational study of late preterm singleton pregnancies at risk of fetal growth restriction (FGR), fetal cerebral Doppler changes were found to be associated with adverse perinatal outcome.

What are the clinical implications of this work?

We confirm an association between abnormal fetal cerebral Doppler and adverse perinatal outcome in late preterm singleton pregnancies at risk of FGR. Whether cerebral flow changes are a marker of fetal compromise and whether intervention changes the risk for poor outcome can be answered only in a randomized intervention study.

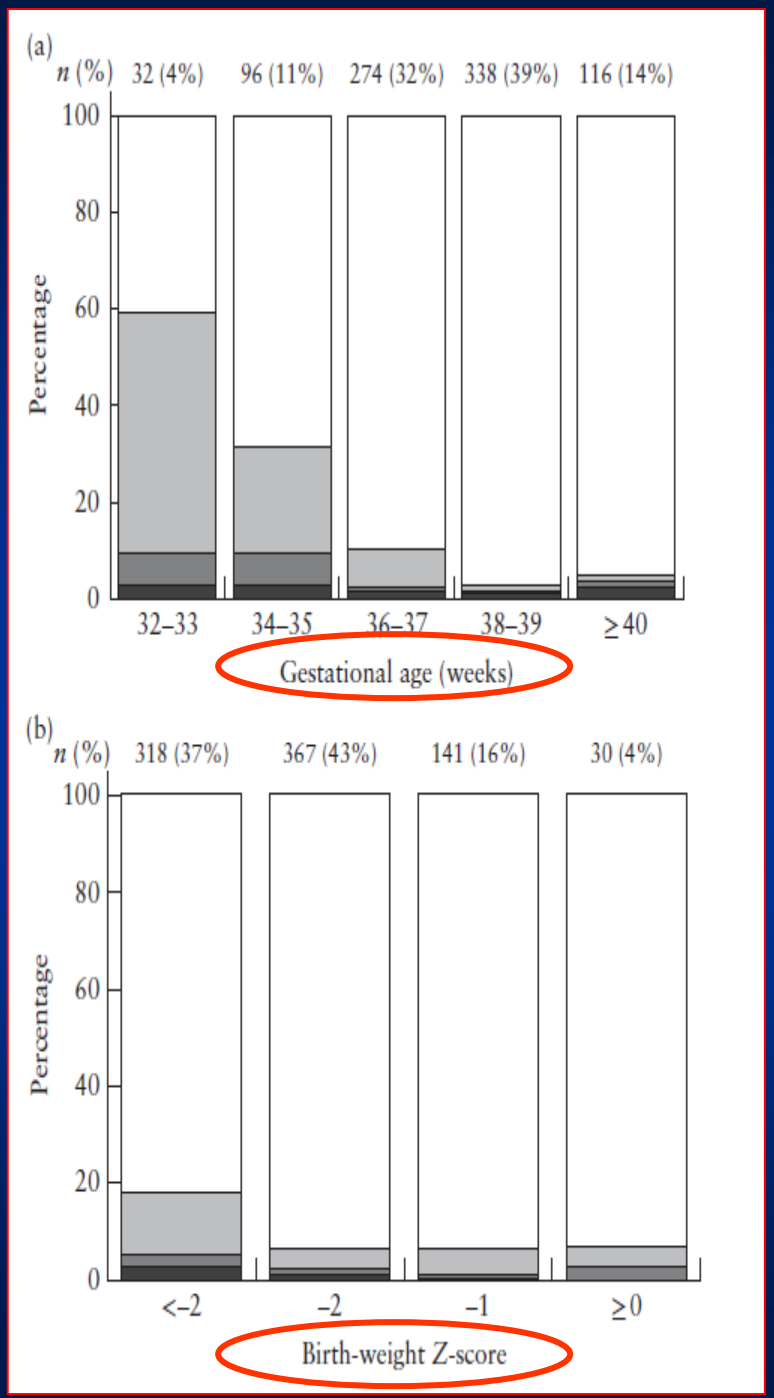


Figure 1 Incidence of composite adverse outcome in 856 late preterm singleton pregnancies at risk of fetal growth restriction, according to gestational age at delivery (a) and birth-weight Z-score (b). Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. Eleven infants had both abnormal condition at birth and major neonatal morbidity. □, normal; ▨, major neonatal morbidity; ▩, abnormal condition at birth + major neonatal morbidity; ■, abnormal condition at birth.

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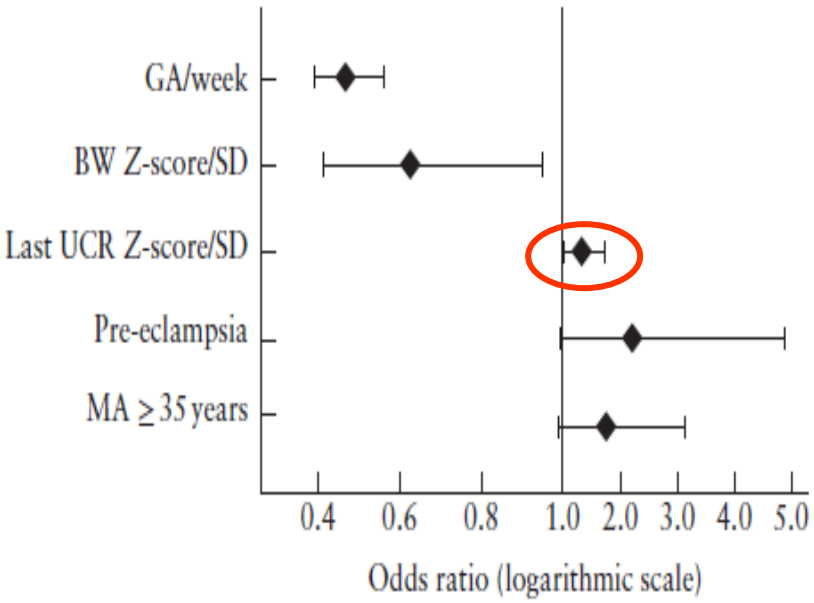

Figure 2 Adjusted odds ratios with 95% CI for composite adverse outcome in 584 late preterm singleton pregnancies at risk of fetal growth restriction and with Doppler measurement obtained within 1 week before delivery, calculated by logistic regression analysis, using parameters that were statistically significant on univariate analysis (Table 3). Missing variables from Table 3 were ejected from analysis when $P > 0.1$. Model had sensitivity of 79% at specificity of 75%, and area under receiver-operating-characteristics curve of 0.84 (95% CI, 0.79–0.89). Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. BW, birth weight; GA, gestational age at delivery; MA, maternal age; UCR, umbilicocerebral ratio.

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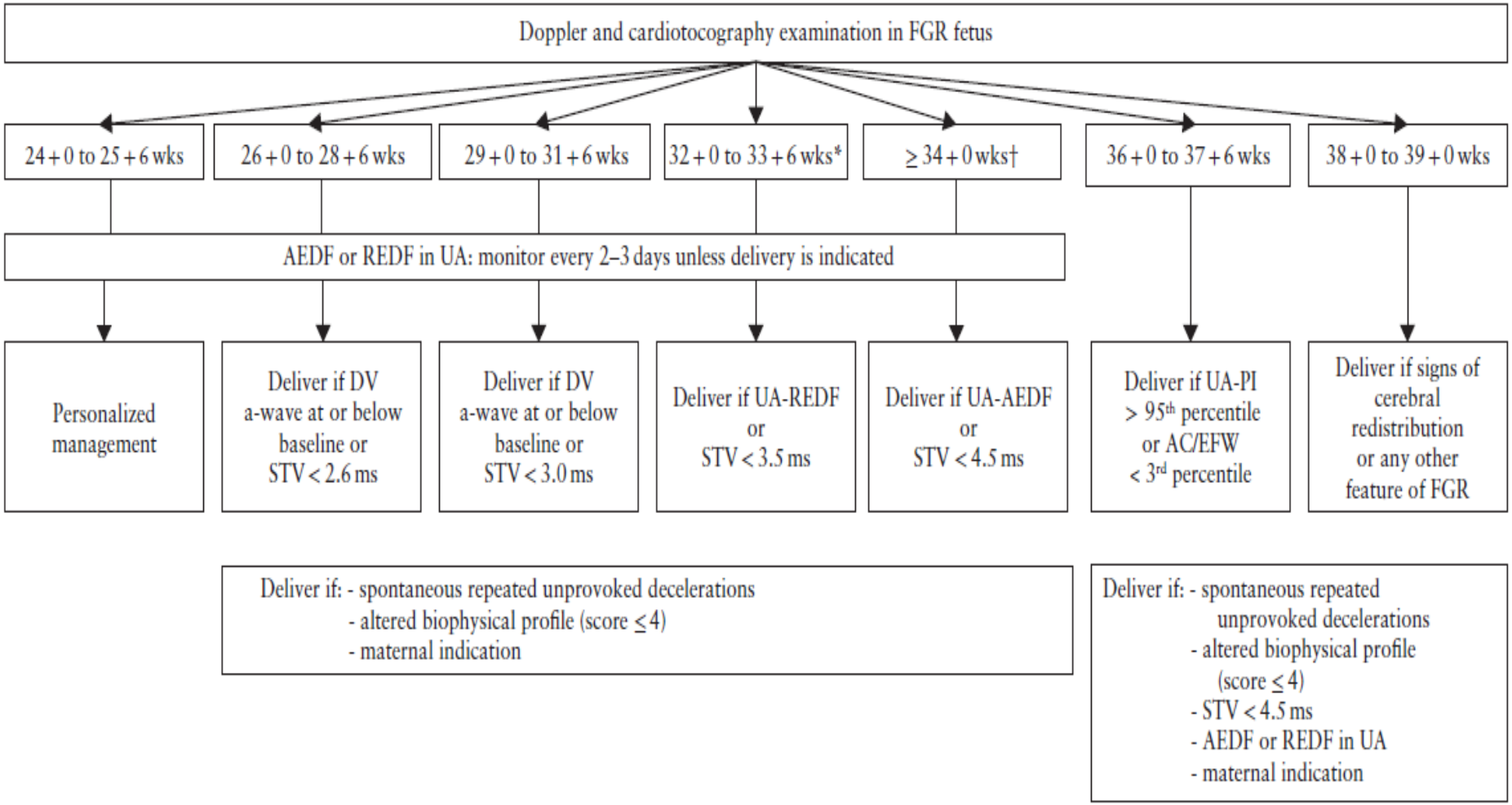
GUIDELINES

ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction

This Guideline should be cited as: 'Lees CC, Stampalija T, Baschat AA, da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, Unterscheider J. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; 56: 298–312.'

Table 1 Main clinical characteristics of early- and late-onset fetal growth restriction (FGR)

Characteristic	*Early-onset FGR*	*Late-onset FGR*
Main clinical challenge	Management	Detection
Prevalence	30%	70%
Gestational age at manifestation	< 32 weeks	≥ 32 weeks
Ultrasound findings	Fetus may be very small	Fetus not necessarily very small
Doppler velocimetry	Spectrum of Doppler alterations that involves umbilical artery, middle cerebral artery and ductus venosus	Cerebral blood-flow redistribution
Biophysical profile	May be abnormal	May be abnormal
Hypertensive disorders of pregnancy	Frequent	Not frequent
Placental histopathological findings	Poor placental implantation, spiral artery abnormalities, maternal vascular malperfusion	Less specific placental findings, mainly altered diffusion
Perinatal mortality	High	Low
Maternal cardiovascular hemodynamic status	Low cardiac output, high peripheral vascular resistance	Less marked maternal cardiovascular findings


Doppler and cardiotocography examination in FGR fetus
24 + 0 to 25 + 6 wks
26 + 0 to 28 + 6 wks
29 + 0 to 31 + 6 wks
32 + 0 to 33 + 6 wks*
≥ 34 + 0 wks†
36 + 0 to 37 + 6 wks
38 + 0 to 39 + 0 wks
AEDF or REDF in UA: monitor every 2–3 days unless delivery is indicated
Personalized management
Deliver if DV a-wave at or below baseline or STV < 2.6 ms
Deliver if DV a-wave at or below baseline or STV < 3.0 ms
Deliver if UA-REDF or STV < 3.5 ms
Deliver if UA-AEDF or STV < 4.5 ms
Deliver if UA-PI > 95th percentile or AC/EFW < 3rd percentile
Deliver if signs of cerebral redistribution or any other feature of FGR
Deliver if: - spontaneous repeated unprovoked decelerations
- altered biophysical profile (score ≤ 4)
- maternal indication
Deliver if: - spontaneous repeated unprovoked decelerations
- altered biophysical profile (score ≤ 4)
- STV < 4.5 ms
- AEDF or REDF in UA
- maternal indication