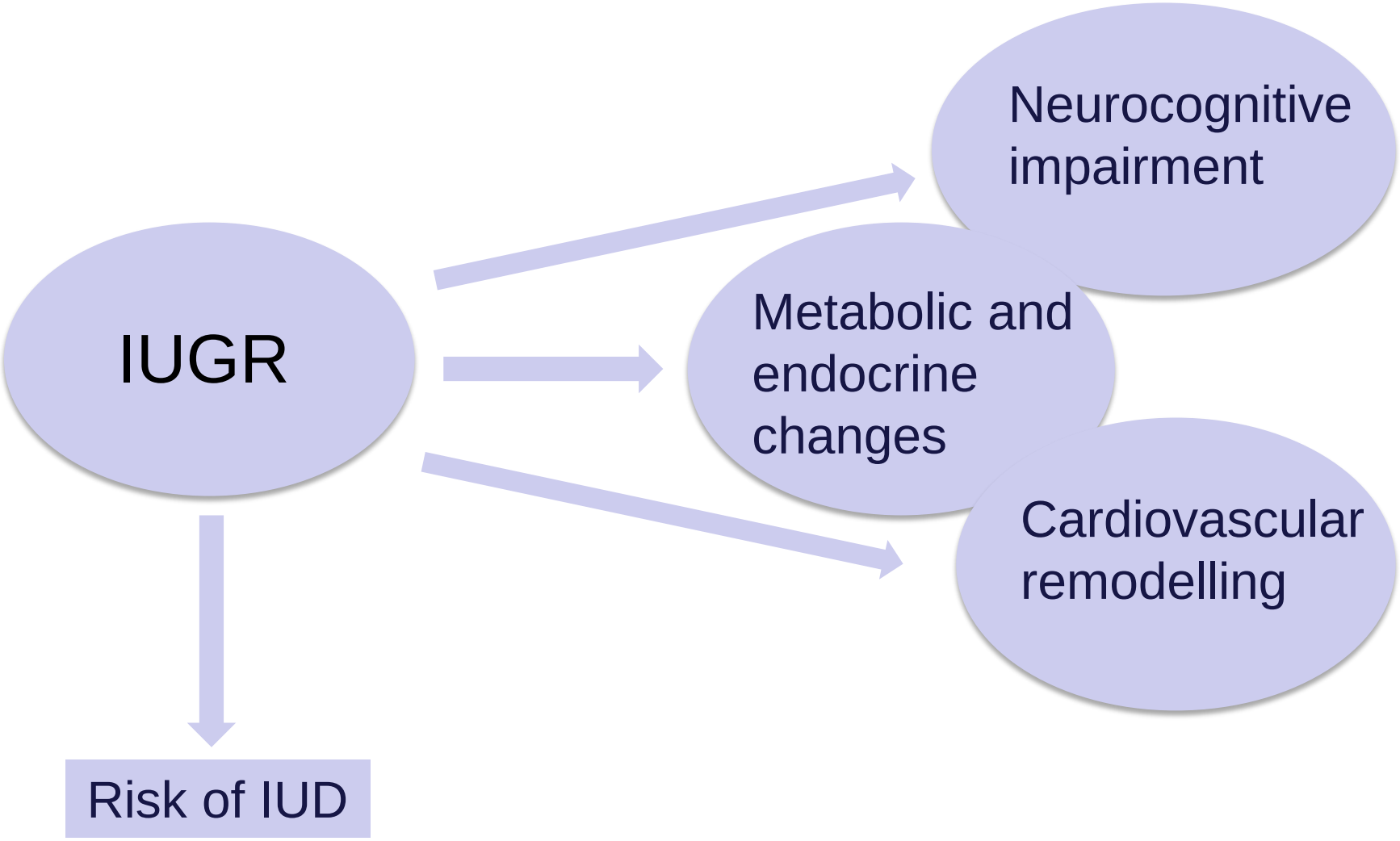
Časná růstová retardace plodu – kdy porodit?

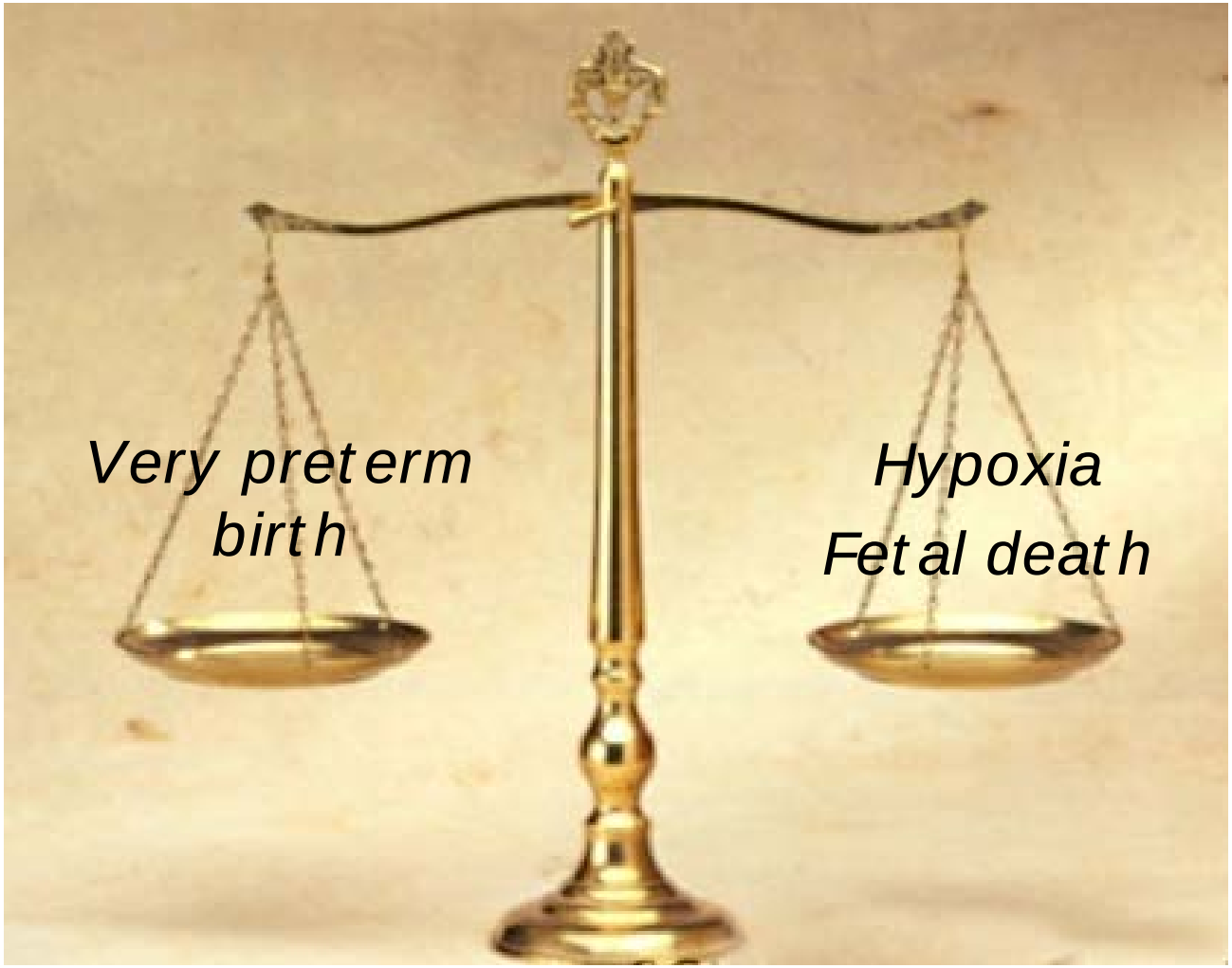
Karel Maršál

LUND
UNIVERSITY


IUGR
Neurocognitive impairment
Metabolic and endocrine changes
Cardiovascular remodelling
Risk of IUD

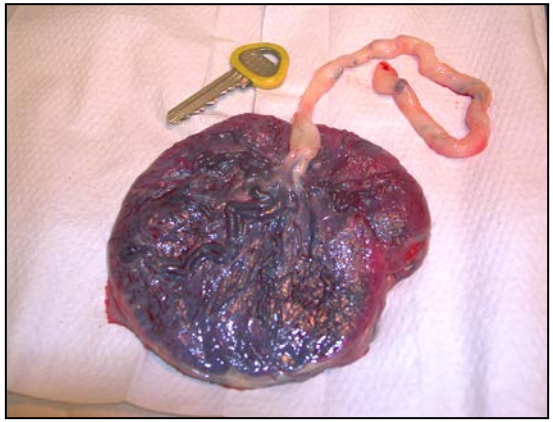
≈ 32 weeks

Early-onset IUGR	Late-onset IUGR
Easy to diagnose	*Difficult to diagnose*
Difficult to manage	*Easy to manage*


Very preterm birth
Hypoxia
Fetal death

Definition of IUGR

SGA fetus with abnormal umbilical artery blood flow velocity



The majority of IUGR cases

is due to placental pathology

Timing of delivery in IUGR according Doppler

(questionnaire among 15 experts)

Table 1. Mean gestational age at which the managing physician opted for delivery, its SD, median and range, and the recommended way of the delivery

FGR	Mean GA	SD	Median GA	Range	Recommended way of delivery
EFW <10th centile, normal Doppler	39.3	1	40	37–41	induction 100%
EFW <3rd centile, normal Doppler	37.8	0.9	38	36–41	induction 100%
Abnormal UtA Doppler	38.2	1.21	38	37–40	induction 100%
Abnormal MCA PI	36.9	1.66	37	34–40	induction 100%
Abnormal CPR	37.4	1.26	37	35–40	induction 100%
UA PI >95th centile	36.36	1.72	37	32–40	induction 100%
UA AEDV	34.64	1.82	34	32–37	induction 50%, elective CS 50%
UA REDV	30.55	3.17	30	25–37	elective CS 100%
UA REDV, DV PI >95th centile	29.82	3.49	28	26–38	elective CS 100%
UA REDV, DV REDV	28.91	3.45	28	25–37	elective CS 100%
UA REDV, BPP <6	26.27	1.6	26	25–34	elective CS 100%
UA REDV, abnormal CTG	29.09	3.4	28	25–38	elective CS 100%

CS = Cesarean Section.

Savchev S et al, Fetal Diagn Ther 2014;36:129–135

Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial

GRIT

The GRIT study group*

Lancet 2004; 364: 513–20

- RCT, 69 hospitals, 13 countries – 548 pregnancies
- randomize when uncertain about the timing of delivery
- ”immediate delivery” vs. ”delay until no uncertainty”
- gest. age at entry (wks) 32 (30-33) vs. 32 (29-34)

- time-to-delivery 0.9 days vs. 4.9 days

- **mortality** 10 % vs. 9 %
  OR 1.1 (95%CI 0.6-1.8)

- **death/severe disability at 2 y** 19 % vs. 16 %
  OR 1.1 (95%CI 0.7-1.8)

Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial

GRIT

The GRIT study group*

Lancet 2004; 364: 513–20

Criticism

- no defined entry criteria
- no management protocol
- unknown number of eligible pregnancies

- no conclusive and generalizable results !

Predictors of Neonatal Outcome in Early-Onset Placental Dysfunction

Baschat et al.

Ahmet A. Baschat, MD, Erich Cosmi, MD, Catarina M. Bilardo, MD, Hans Wolf, MD, Christoph Berg, MD, Serena Rigano, MD, Ute Germer, MD, Dolores Moyano, MD, Sifa Turan, MD, John Hartung, MD, Amarnath Bhide, MD, Thomas Müller, MD, Sarah Bower, MD, Kypros H. Nicolaides, MD, Baskaran Thilaganathan, MD, Ulrich Gembruch, MD, Enrico Ferrazzi, MD, Kurt Hecher, MD, Henry L. Galan, MD, and Chris R. Harman, MD

OBSTETRICS & GYNECOLOGY VOL. 109, NO. 2, PART 1, FEBRUARY 2007

- multicenter observational study
- 604 liveborn newborns with prenatally diagnosed IUGR
- < 33 gestational weeks (median 29 wks)

- **major morbidity** 36 %
- IVH 15 %
- NEC 12 %

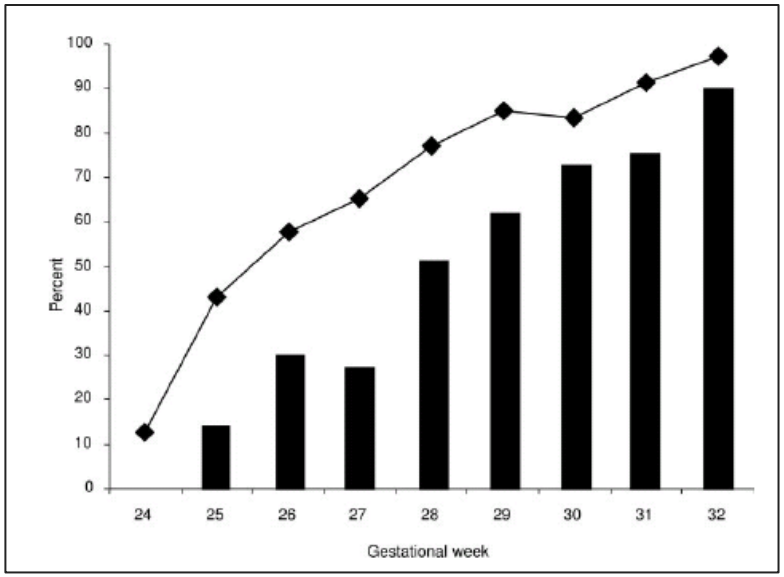
- **mortality** 21 %

- **intact survival** **58 %**

Predictors of Neonatal Outcome in Early-Onset Placental Dysfunction

Baschat et al.

OBSTETRICS & GYNECOLOGY VOL. 109, NO. 2, PART 1, FEBRUARY 2007



Neonatal survival (black diamonds) and intact survival rates (black bars) per gestational week with advancing gestational week.

Conclusion

Gestational age and the birth weight are the primary quantifying parameters. Beyond these thresholds, ductus venosus Doppler parameters emerge as the primary cardiovascular factor in predicting neonatal outcome.

Baschat A et al.
Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters.
Ultrasound Obstet Gynecol 2009; **33**: 44–50

Baschat et al.

- single center, 113 patients, 25-37 wks, 2-year follow-up

Conclusion

UA-REDV is an independent contributor to poor neuro-development. Gestational age and birth weight remain the predominant factors for poor neurodevelopment in IUGR.

Criticism

Patients were delivered for maternal indications or an abnormal biophysical profile

- 20 % acidemia
- 26 % perinatal mortality
- 39 % major neonatal morbidity

Delivered too late !

Early intervention in management of very preterm growth-restricted fetuses: 2-year outcome of infants delivered on fetal indication before 30 gestational weeks

J. BRODSZKI*, E. MORSING†, P. MALCUS*, A. THURING*, D. LEY† and K. MARŠÁL*

Ultrasound Obstet Gynecol 2009; 34: 288–296

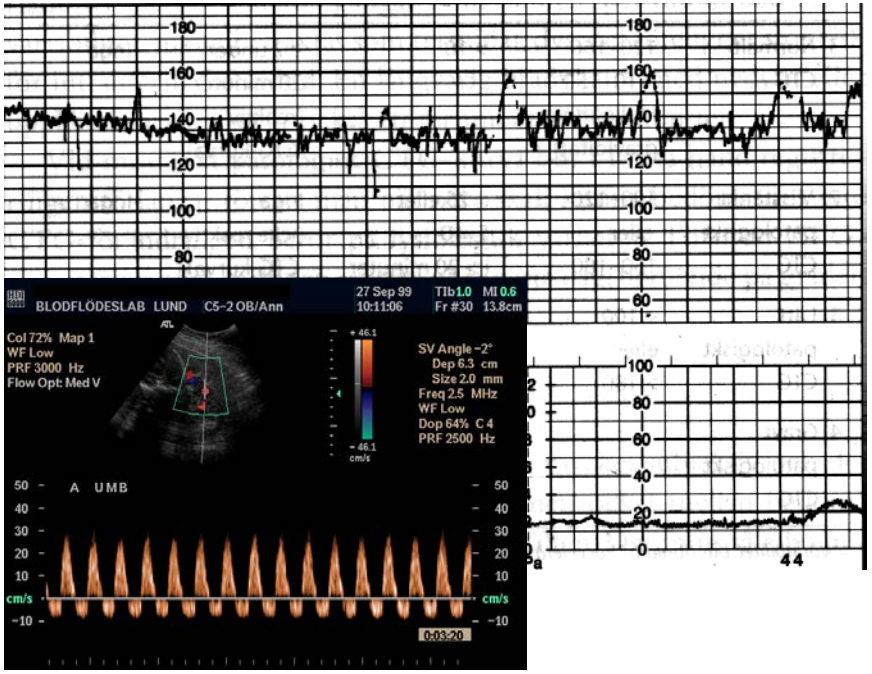
Lund University

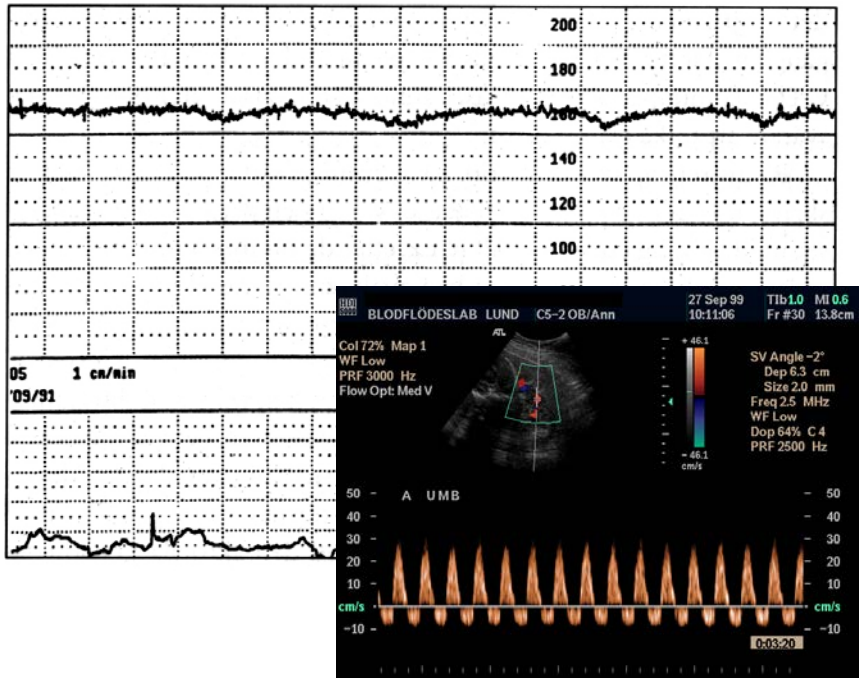
Follow-up studies of growth restricted fetuses

Consequences for the obstetric management based on Doppler velocimetry ?

More active obstetric management !

IUGR fetus



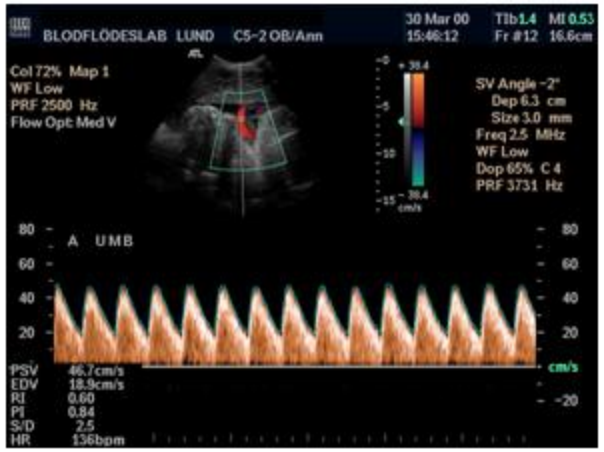


Good prognosis

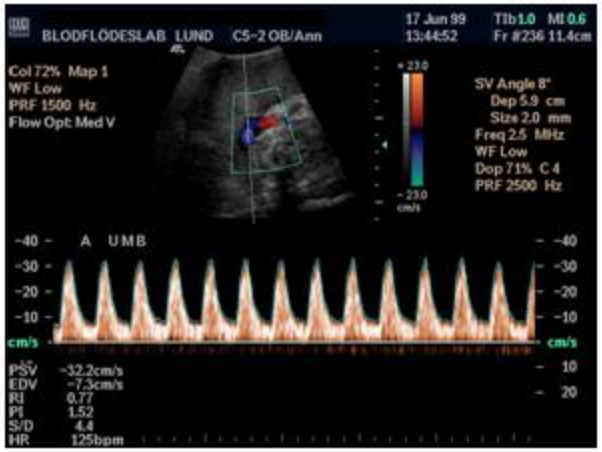
Bad prognosis

BLOOD FLOW CLASSES (BFC)

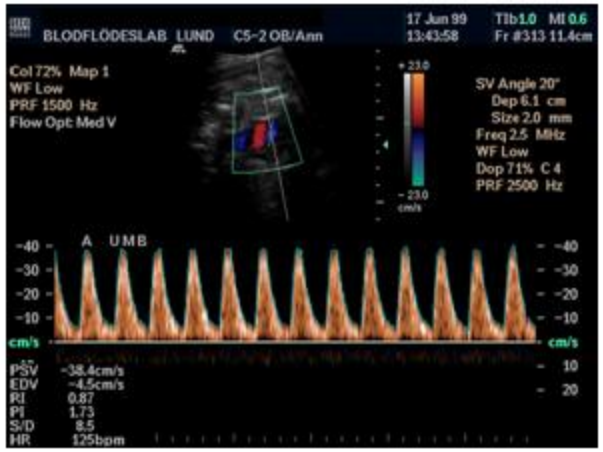
BFC normal



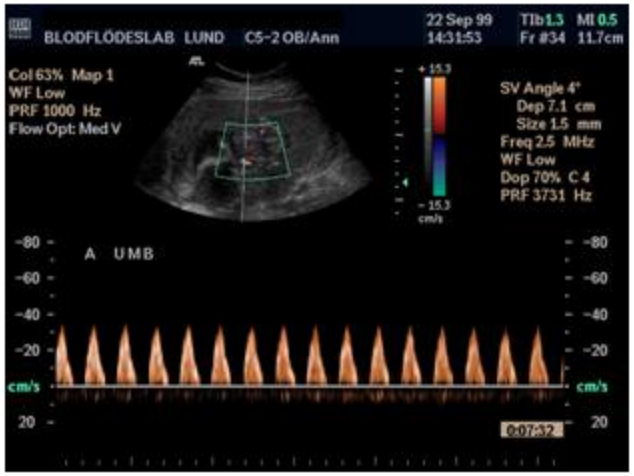
BFC I



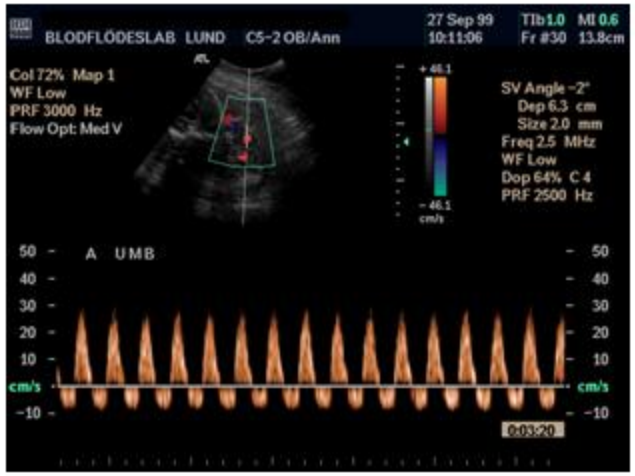
BFC II



BFC III A

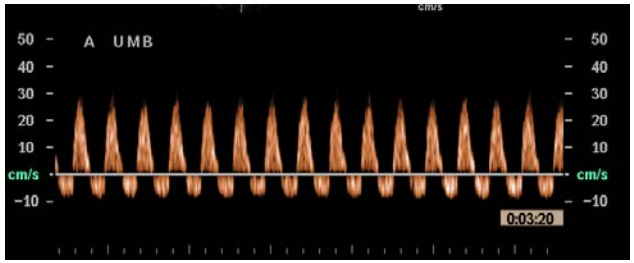


BFC III B

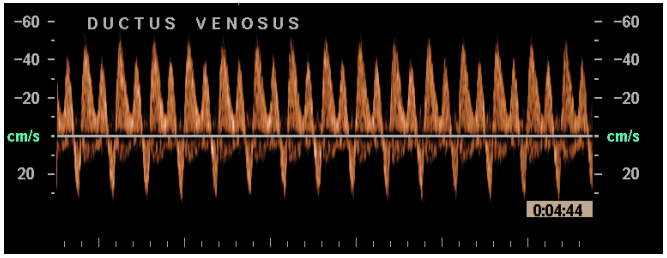


IUGR fetus < 30 gest. weeks

- delivery at the occurrence of reverse diastolic flow in the umb. artery or if rapid progress in the ductus venosus Doppler



or



- before the occurrence of FHR pathology !

Early intervention in management of very preterm growth-restricted fetuses: 2-year outcome of infants delivered on fetal indication before 30 gestational weeks

J. BRODSZKI*, E. MORSING†, P. MALCUS*, A. THURING*, D. LEY† and K. MARŠÁL*

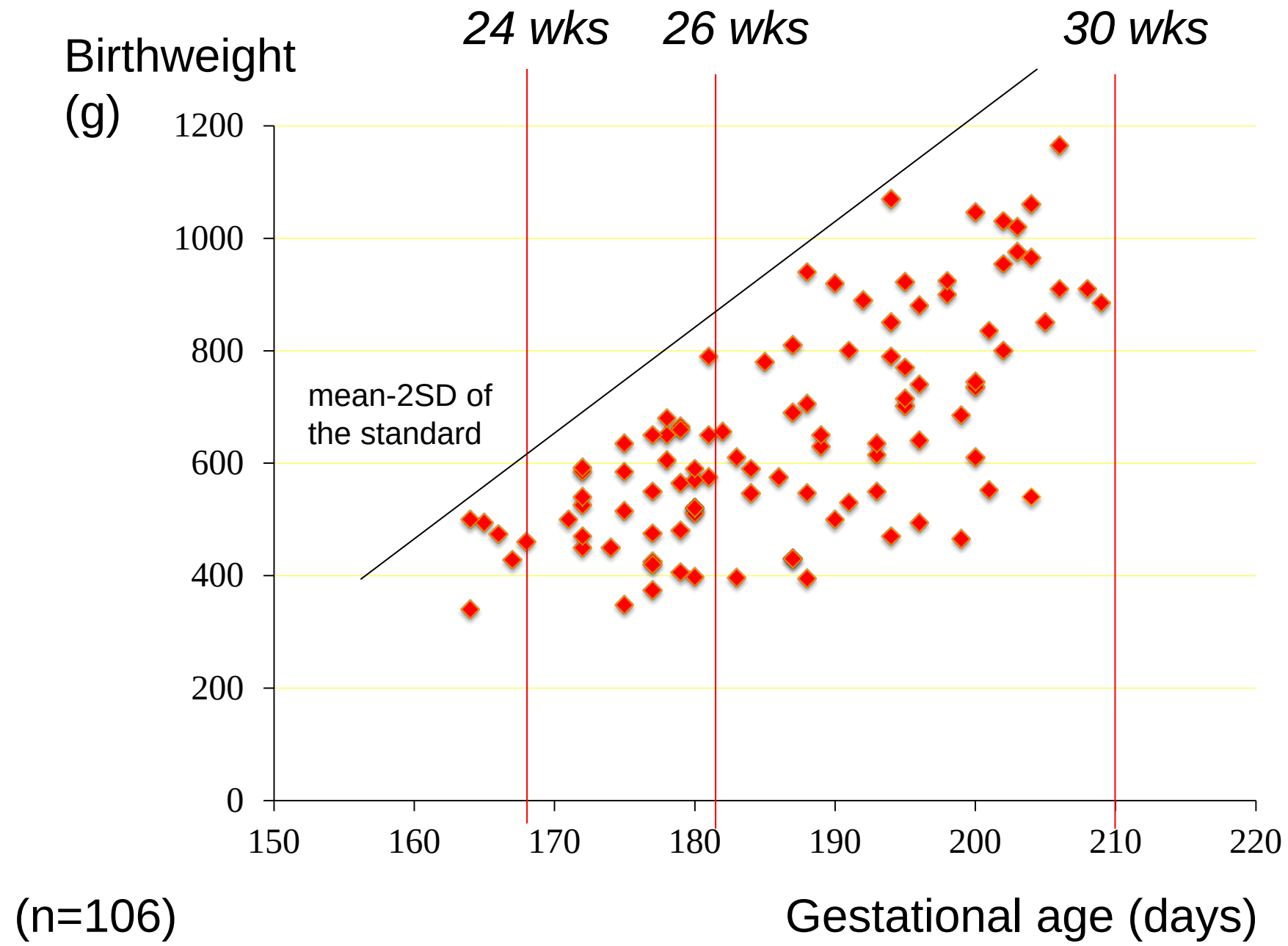
Ultrasound Obstet Gynecol 2009; 34: 288–296

Lund University

- single center observational study
- 46 IUGR fetuses with umb. artery ARED flow
- delivered < 30 gestational weeks

- IUD 9 %
- survival 2 years 90 %

Conclusions *Very preterm growth-restricted fetuses with umbilical artery ARED delivered on fetal indication, in most cases before the occurrence of severe changes in the ductus venosus velocity waveforms and/or fetal heart rate tracings, showed high 2-year survival and low morbidity.*


24 wks
26 wks
30 wks
Birthweight (g)
1200
1000
800
600
400
200
0
mean-2SD of the standard
150
160
170
180
190
200
210
220
(n=106)
Gestational age (days)

Very preterm IUGR

Lund University

Lund 1998-2011 – 106 fetuses with ARED blood flow delivered <30 gest. wks

Perinatal outcome

N (%)	ARED n=106	Controls n=830	
Perinatal mortality	7 (6.6 %)	114 (13.7 %)	*p=0.04*
Stillbirths	4 (3.8 %)	57 (6.85 %)	
Deaths <7 days	3 (2.8 %)	57 (6.85 %)	
Liveborn	102	773	

Very preterm IUGR

Lund University

Pregnancy outcome

Liveborn (n=102)		
Antenat. steroids	94	[92 %]
Cesarean section	102	[100 %]
Gestational age at birth (wks+days)	26+5	(23+3 – 29+6)
Birth weight (g)	610	(340 - 1165)
Singletons/Twins	78 / 24	[76% / 24%]

Lund University

Outcome at 2 years of age

	IUGR n=102	Control n=773	*P*
Survival	86 %	85 %	*ns*
Cerebral palsy	9 %	8 %	*ns*

Follow-up at 6 years of age

Lund University

Neurodevelopment, lung and cardiovascular function, brain MRI (38 preterm IUGR, 38 preterm & 38 term matched controls)

- No increase in CP but more frequent need for habilitation service
- Reduced cognitive function in boys
- Reduced lung function
- Reduced brain volumes – not associated with functional deficits

Lund University

Nevertheless !

Compared to preterm controls the observed outcomes in preterm IUGR were not sufficiently severe to refrain from delivery

Very preterm IUGR fetuses with abnormal flow in the umbilical artery

Reference	Liveborn n	Gestational age - inclusion	Survival
Schwarze et al. UOG 2005	53	<32 wks	89 %
Hartung et al. UOG 2005	11	<29 wks	64 %
Baschat et al. UOG 2007	326	<30 wks	69 %
Mari et al. JUM 2007	34	≤32 wks	71 %
Brodszki et al. UOG 2009	42	24 - 29 wks	90 %
Lund 1998-2011	102	23 – 29 wks	86 %
Lees et al. *(TRUFFLE)* UOG 2013	503	26 - 32 wks	92 %

The European ***multicentric randomized trial***

T*RIAL*
R*ANDOMIZING*
U*MBILICAL and*
F*ETAL*
FL*OW in*
E*UROPE*

Lees et al. 2013

Ultrasound Obstet Gynecol 2013; **42**: 400–408
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.13190

TRUFFLE

Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE)

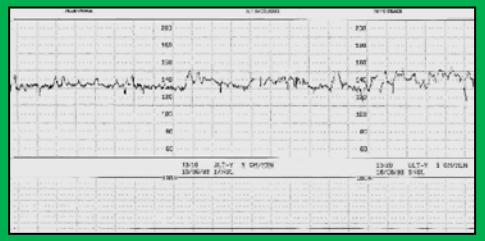
C. LEES[1], N. MARLOW[2], B. ARABIN[3], C. M. BILARDO[4], C. BREZINKA[5], J. B. DERKS[6], J. DUVEKOT[7], T. FRUSCA[8], A. DIEMERT[9], E. FERRAZZI[10], W. GANZEVOORT[11], K. HECHER[9], P. MARTINELLI[12], E. OSTERMAYER[13], A. T. PAPAGEORGHIOU[14], D. SCHLEMBACH[15], K. T. M. SCHNEIDER[13], B. THILAGANATHAN[14],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

- RCT, 20 hospitals, 5 countries in 2005-2010
- 503 pregnancies
- entry criteria
    - singleton
    - 26 – 32 weeks
    - abd. circumference <10th centile
    - EFW >500 g
    - umb. artery PI<95th centile and normal DV PI
    - normal FHR short-term variability (STV)

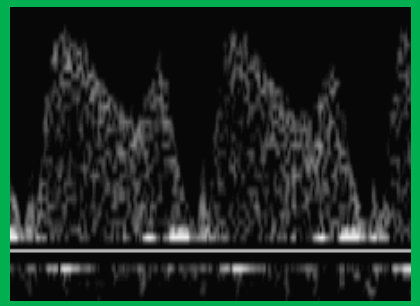
TRUFFLE study

Randomized management study in IUGR

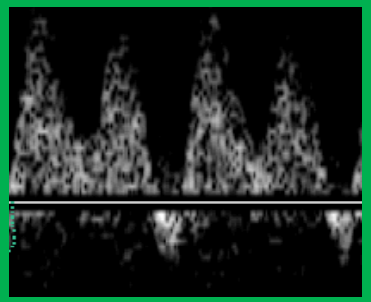
Computerized CTG



Early ductus changes



Late ductus changes



All groups as safety net - computerized CTG (STV)
- umbilical artery Doppler (after 30+0 wks)

Lees et al. 2013

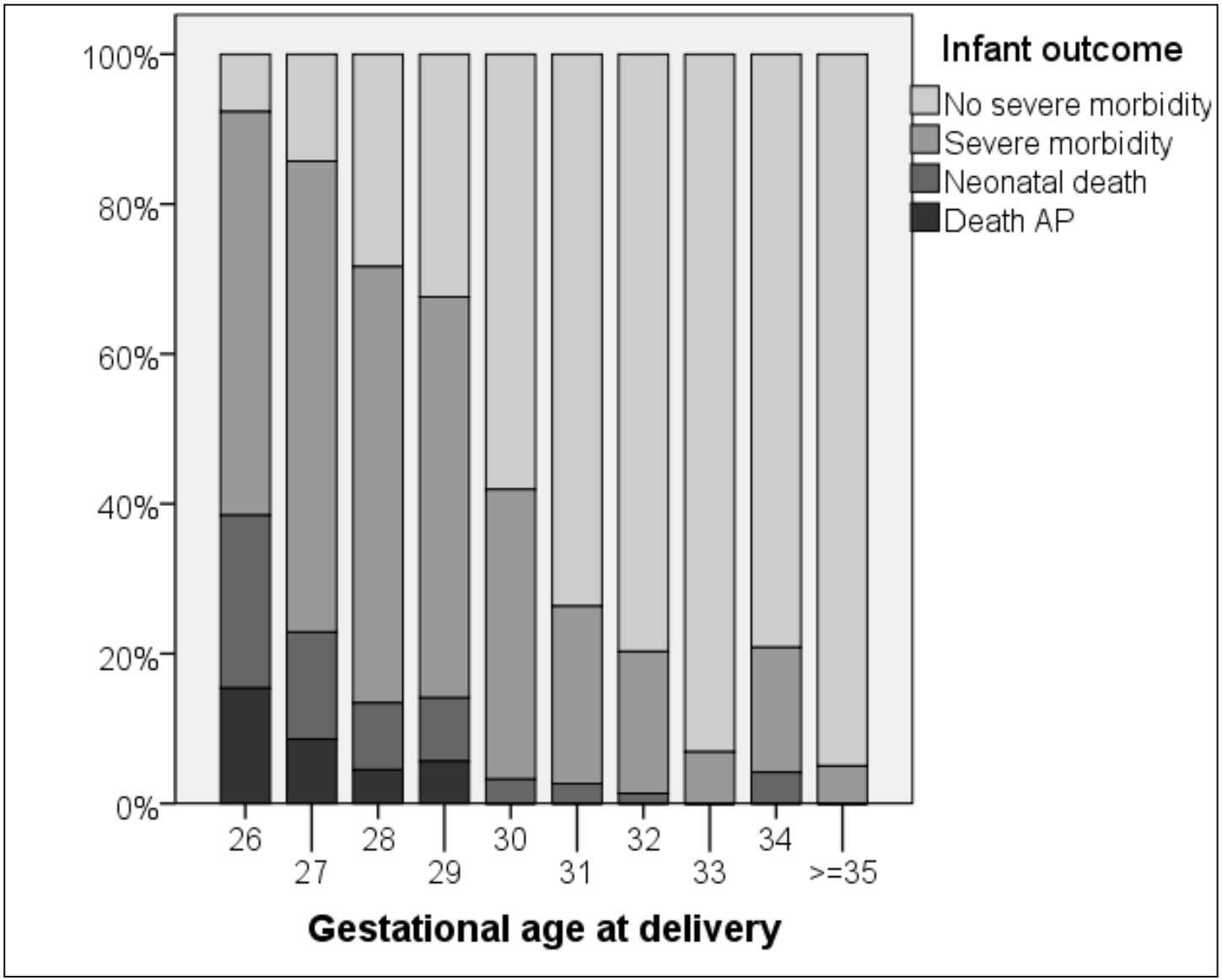
TRUFFLE

Short term morbidity & mortality

	Total
Total	**503**
Fetal death No intervention*	5 (1%)
Unexpected#	7 (1%)
Live birth	491 (97%)
Neonatal death	27 (6%)
Death due to congenital abnormality	2
Overall mortality	39 (8%)
Neonatal data missing	1 (0%)
Survival at discharge	463 (92%)

Lees et al. 2013

TRUFFLE



Lees 2014

TRUFFLE

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

- analysis acc. to randomization
  - STV n=166
  - early DV n=167
  - late DV n=170

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

TRUFFLE

Neonatal morbidity	CTG STV	DV PI 95th	DV no A		TOTAL
Received mechanical ventilation	72 (44%)	63 (39%)	69 (42%)		204 (42%)
Received supplemental oxygen	98 (60%)	96 (59%)	103 (63%)		297 (61%)
BPD >28 days	32 (20%)	28 (17%)	31 (19%)		91 (19%)
BPD >36 weeks †	16 (10%)	17 (10%)	16 (10%)		49 (10%)
Sepsis (Proven) †	33 (20%)	31 (19%)	23 (14%)		87 (18%)
NEC Pneumatosis †	3 (2%)	3 (2%)	1 (1%)		7 (1%)
Perforation †	2 (1%)	2 (1%)	5 (3%)		9 (2%)
GMH Grade III or IV †	0 (--%)	4 (2%)	8 (5%)		12 (2%)
PVL Grade II or III †	1 (1%)	2 (1%)	2 (1%)		5 (1%)
Death following severe morbidity †	10 (6%)	6 (4%)	9 (5%)		25 (5%)
Adjusted age of survivors at discharge in days ‡	-9 (-39 to 170)	-7 (-37 to 99)	-10 (-38 to 169)		–9 (–39 to 170)
Survival following severe neonatal morbidity (% of survivors) †	38 (25%)	42 (27%)	38 (25%)		118 (25%)
Survival without severe neonatal morbidity (% of all study entrants)	115 (69%)	115 (69%)	115 (68%)		345 (69%)

No differences between the groups for morbidity

Lees C 2015

TRUFFLE

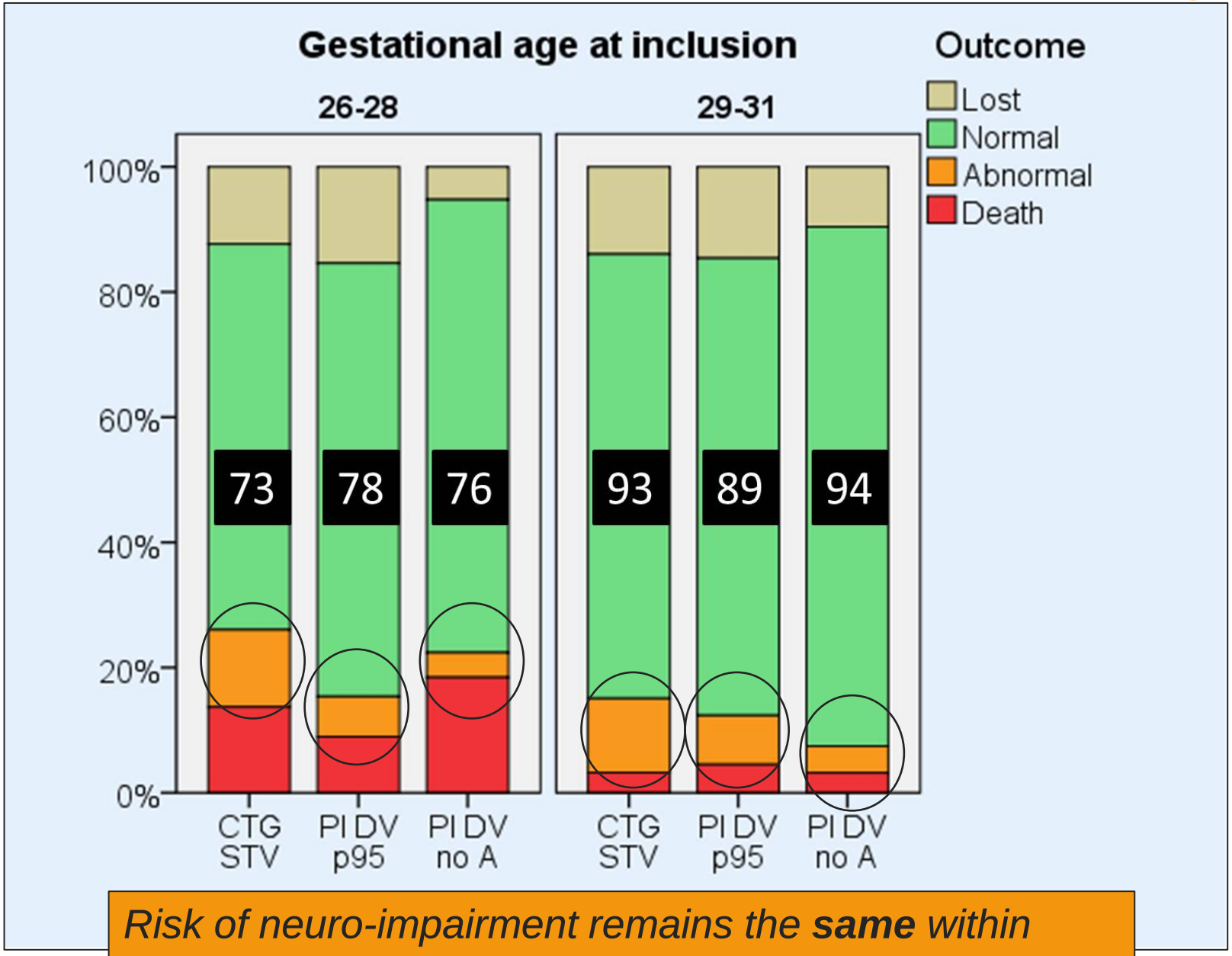
Composite primary outcome at 2 years of age

	CTG STV	DV p95	DV no A		Total
Study group at inclusion	166	167	170		503
Infants with known outcome*	144 (87%)	142 (85%)	157 (92%)		443 (88%)
Survivors evaluated for neuro-development**	131 (86%)	131 (84%)	140 (92%)		402 (87%)
Survival without impairment					
Percentage of evaluated surviving infants [a]	111 (85%)	119 (91%)	133 (95%)		363 (90%)
Percentage of all infants with known outcome [b]	(77%)	(84%)	(85%)		(82%)

[&] Includes adjusted Bayley 2 MDI scores (MDI + 5points)
a Linear association p = 0.004; Chi-square DVnoA vs CTG-STV p = 0.005
b Linear association p = 0.09; Chi-square DVnoA vs CTG-STV p = 0.09
* Percentage of all infants
** Percentage of surviving infants
[#] Percentage of evaluated infants

Lees C 2015

TRUFFLE

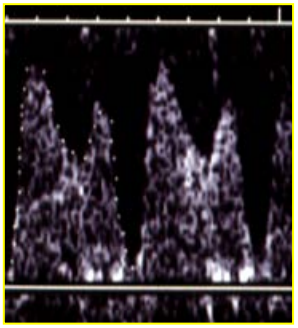


*Risk of neuro-impairment remains the **same** within randomized group & is **unrelated** to inclusion gestation*

Lees C 2014

Main findings :

TRUFFLE



<32 weeks, management based on ductus venosus:

Lower risk of neuroimpairment

- if delivery is based on absent or reversed DV 'a' wave

OR

- on CTG STV severely abnormal

Better neurodevelopmental outcome if you wait for late DV changes, but a slightly higher risk of perinatal death.

Lees C 2014

Differences between Lund and TRUFFLE studies

	Lund	TRUFFLE
Pregnancies	singletons and multiples	singletons
GA at entry (wks + d)	25+3 (23+3 – 29+6)	29+1 (26+0 – 31+6)
GA at delivery (wks + d)	26+5 (23+4 – 29+6)	30+5 (27+1 – 38+4)
Birth weight (g)	642 (395 – 1165)	mean 1013 ±SD ±321

median (range)

Comparative study Lund vs. TRUFFLE

(in progress)

Selection of comparable sub-cohorts:

- singletons
- gestational age at entry 26+0-29+6 weeks
- ARED flow in umbilical artery
- birth weight <mean-2SD

Primary outcome:

1. survival at 2 years
2. survival without neurodevelopmental impairment

Hypothesis:

Umbilical artery Doppler as surveillance tool in very preterm IUGR is as effective as DV Doppler and STV

Comparative study Lund vs. TRUFFLE
(in progress)

Neurodevelopmental impairment (NDI)

Criteria for NDI as infant and as child

Age:	2y	>3y
GMFCS (cerebral palsy)	3-5	2-5
Bayley/IQ	<85 (B3)	<70 (IQ)
Hearing	Aids or worse	Aids or worse
Vision	Blind/sees light only	Blind/sees light only

Comparative study Lund vs. TRUFFLE
(in progress)

	Lund	TRUFFLE	p-value
n	49	127	
GA at delivery, weeks	27+6	28+4	0.0003
median (range)	(26+0-29+6)	(26+1-29+6)	
Male gender, n (%)	28 (57%)	64 (55%)	n.s.
Birth weight, g, mean ±SD	732 ±187	738 ±149	n.s.
Apgar score <7 at 5 min, n (%)	10 (20%)	21 (18%)	n.s.
Apgar score <4 at 5 min, n (%)	0	9 (8%)	0.06
Fetal death, n (%)	0	10 (8%)	0.06
Neonatal death, n/N (%)	1/49 (2%)	15/117 (13%)	0.04
Survival at 2 years (of all), n (%)	46 (94%)	102 (80%)	0.04
Survival without NDI (of live-born), n/N (%)	37/45 (82%)	78/92 (85%)	n.s.

Comparative study Lund vs. TRUFFLE
(in progress)

	Lund	TRUFFLE DV no A-wave	p-value
n	49	43	
GA at delivery, weeks median (range)	27+6 (26+0-29+6)	28+5 (26+1-29+6)	0.0005
Fetal death, n (%)	0	4 (9%)	0.04
Neonatal death, n/N (%)	1/49 (2%)	5/39 (13%)	n.s.
Survival at 2 years (of all), n (%)	46 (94%)	34 (79%)	0.06
Survival without NDI (of live-born), n/N (%)	37/45 (82%)	30/33 (91%)	n.s.

Comparative study Lund vs. TRUFFLE
(in progress)

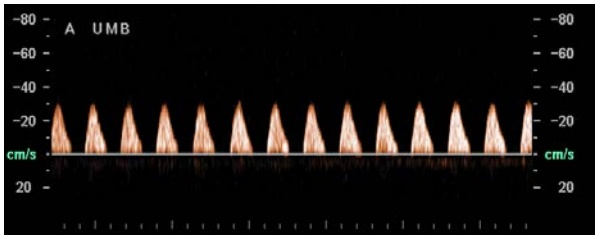
Conclusion

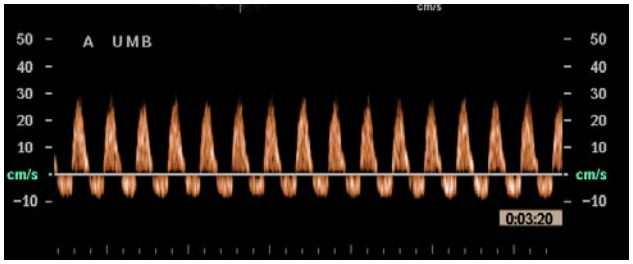
The use of umbilical artery Doppler in monitoring very preterm IUGR fetuses (<30 weeks) led to fewer fetal and neonatal deaths and to a higher survival at 2 years of age than did the use of ductus venosus Doppler or CTG short-term variability.

There was no difference in the postnatal neurodevelopment.

Take home messages from the Lund and TRUFFLE studies

- **Active management of very preterm IUGR** is associated with improved survival
- The long-term outcome is not worse than that in very preterm infants with normal growth (AGA)
- All available infomation on fetal condition is of importance (Doppler, CTG – preferably computerized, growth etc.)
- **Longitudinal development** of Doppler findings is important
- The most important fetoplacental Doppler parameters: **umbilical artery**, umbilical vein, ductus venosus, CTG STV

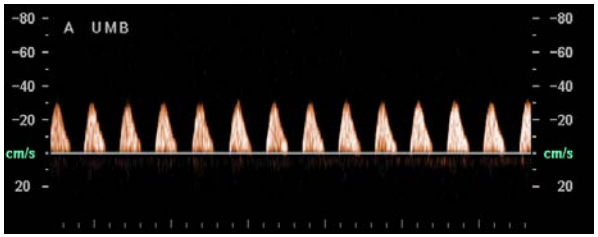




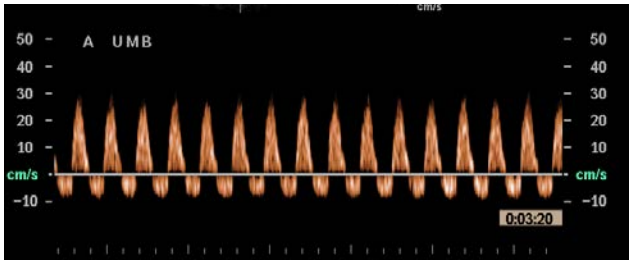
Absent or reverse EDF at 23-24 wks

- FHR without severe pathology
- ductus venosus without reverse flow

- hospitalization
- Doppler daily
- CTG several times a day
- steroid treatment



≥ 25+0 wks



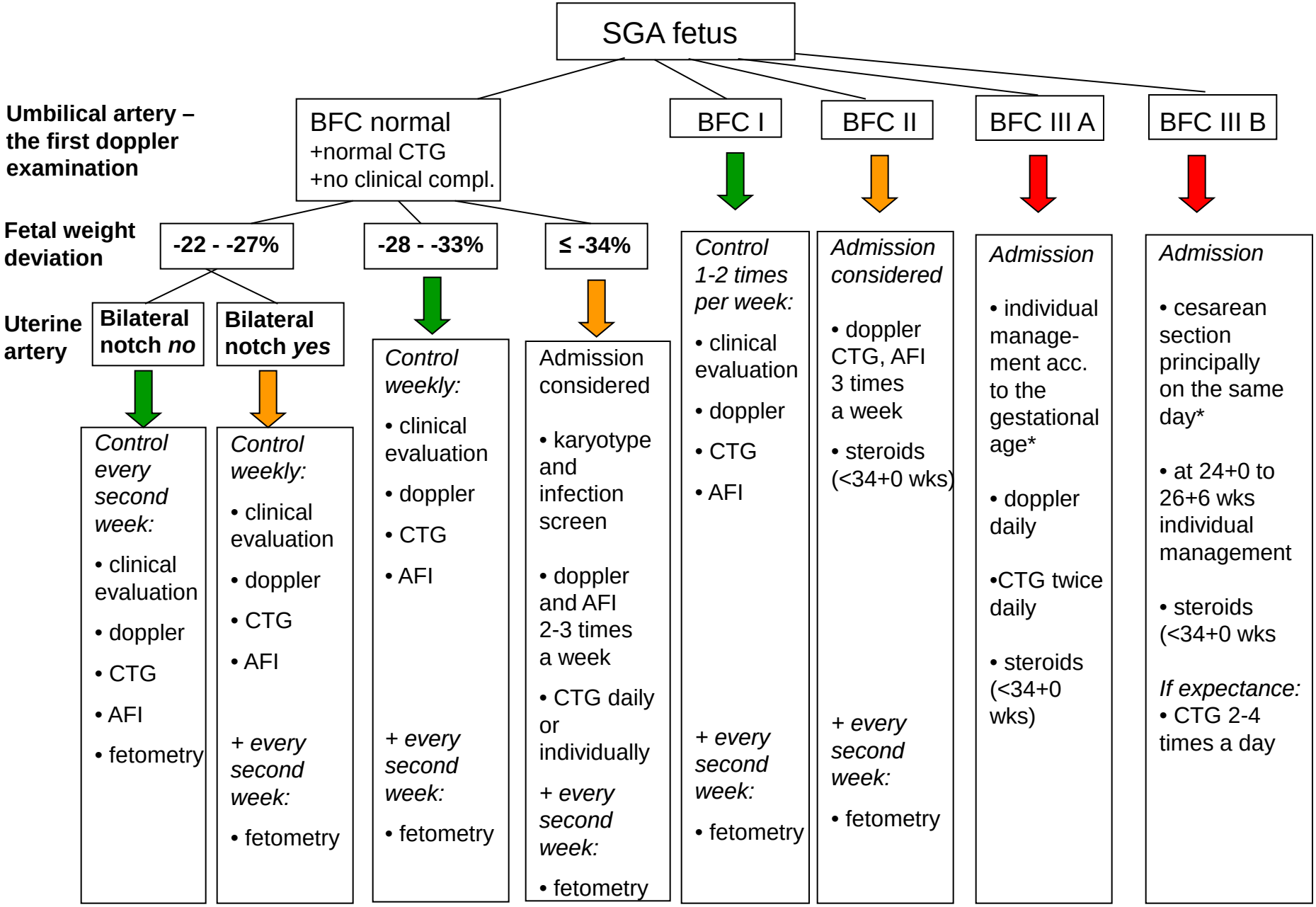
Absent EDF

- hospitalization
- steroid treatment
- CTG several times a day
- Doppler daily

Reverse EDF

- steroids
- delivery most often within 24 hrs

Delivery if abnormal findings in the FHR or DV, or if change to Reverse EDF



*Pulsations in the umbilical vein and/or abnormal ductus venosus waveform = contributing indication to delivery