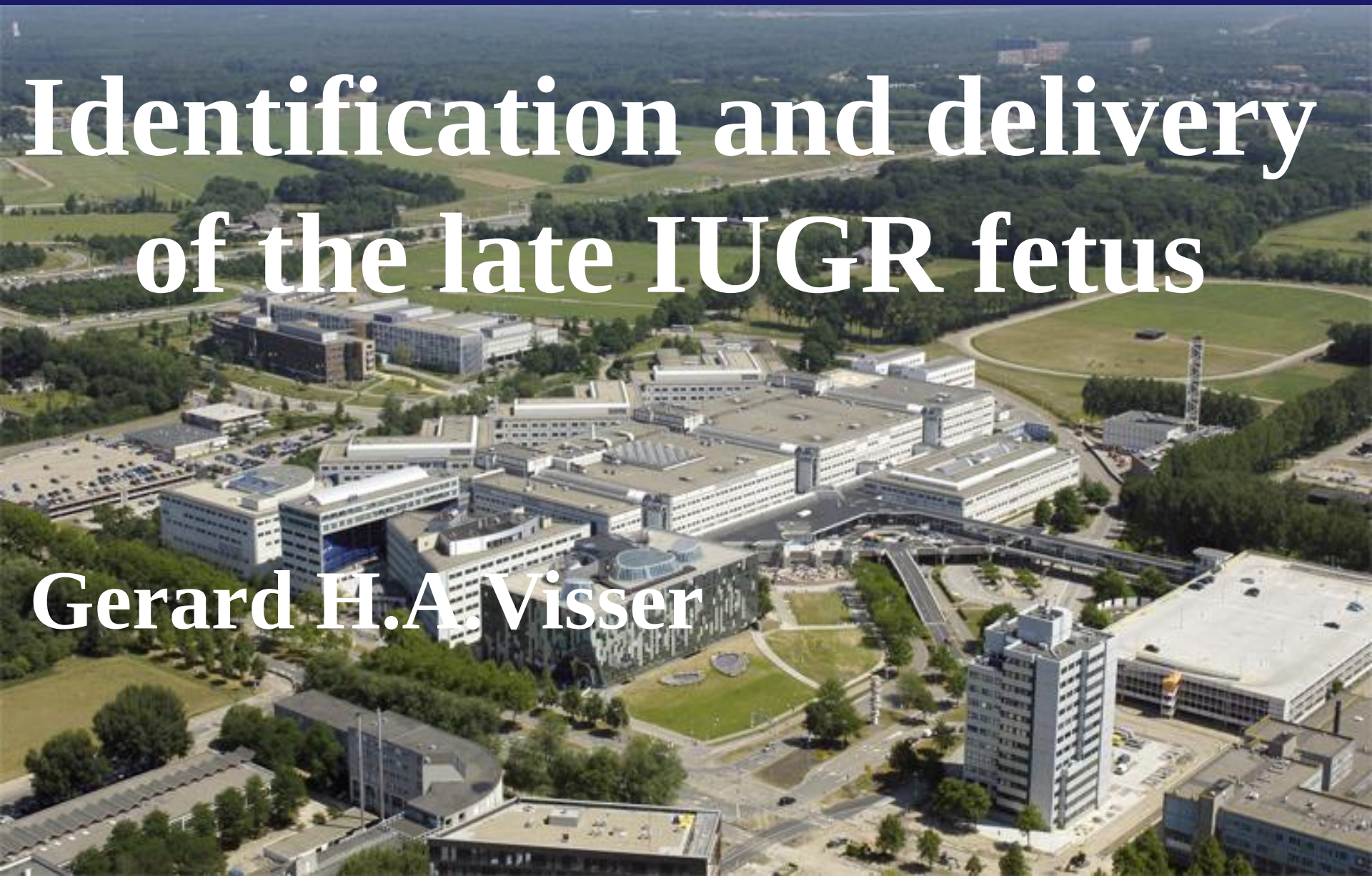
University Medical Center, Utrecht, the NL

Identification and delivery of the late IUGR fetus

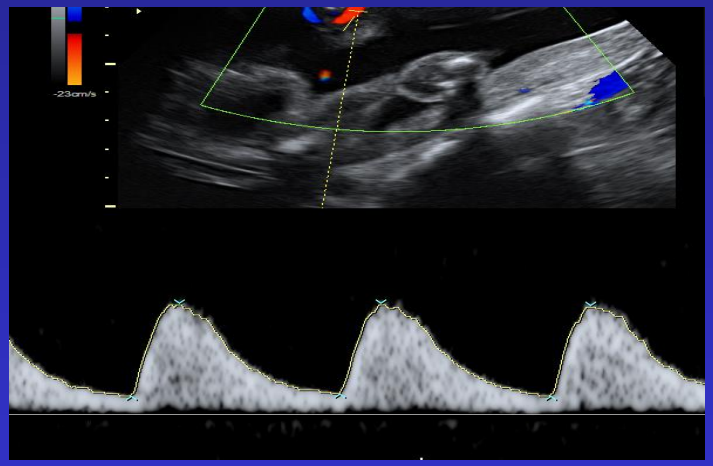


Gerard H.A. Visser

Term IUGR/SFD

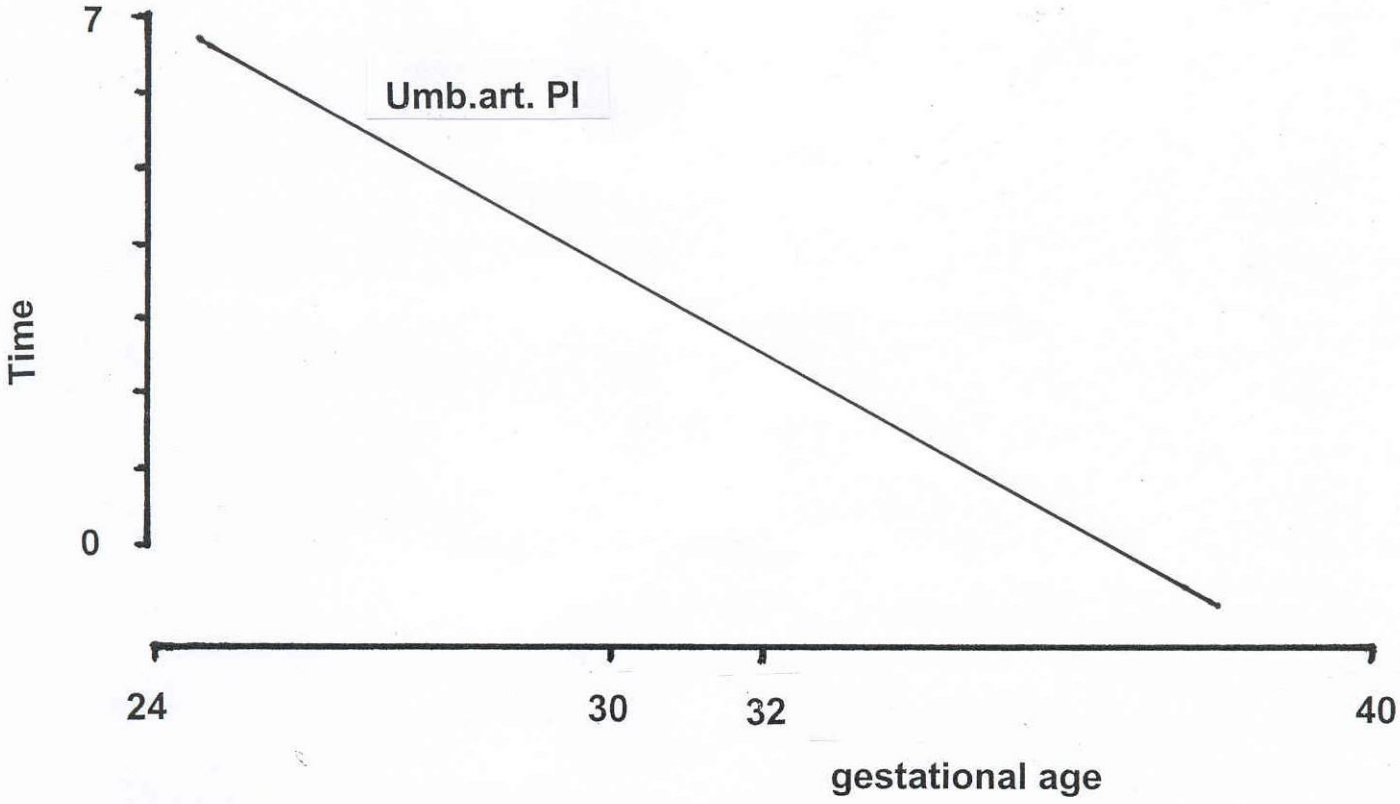
Many screening and diagnostic tests do not work properly

(and that holds especially for Doppler umbilical artery)



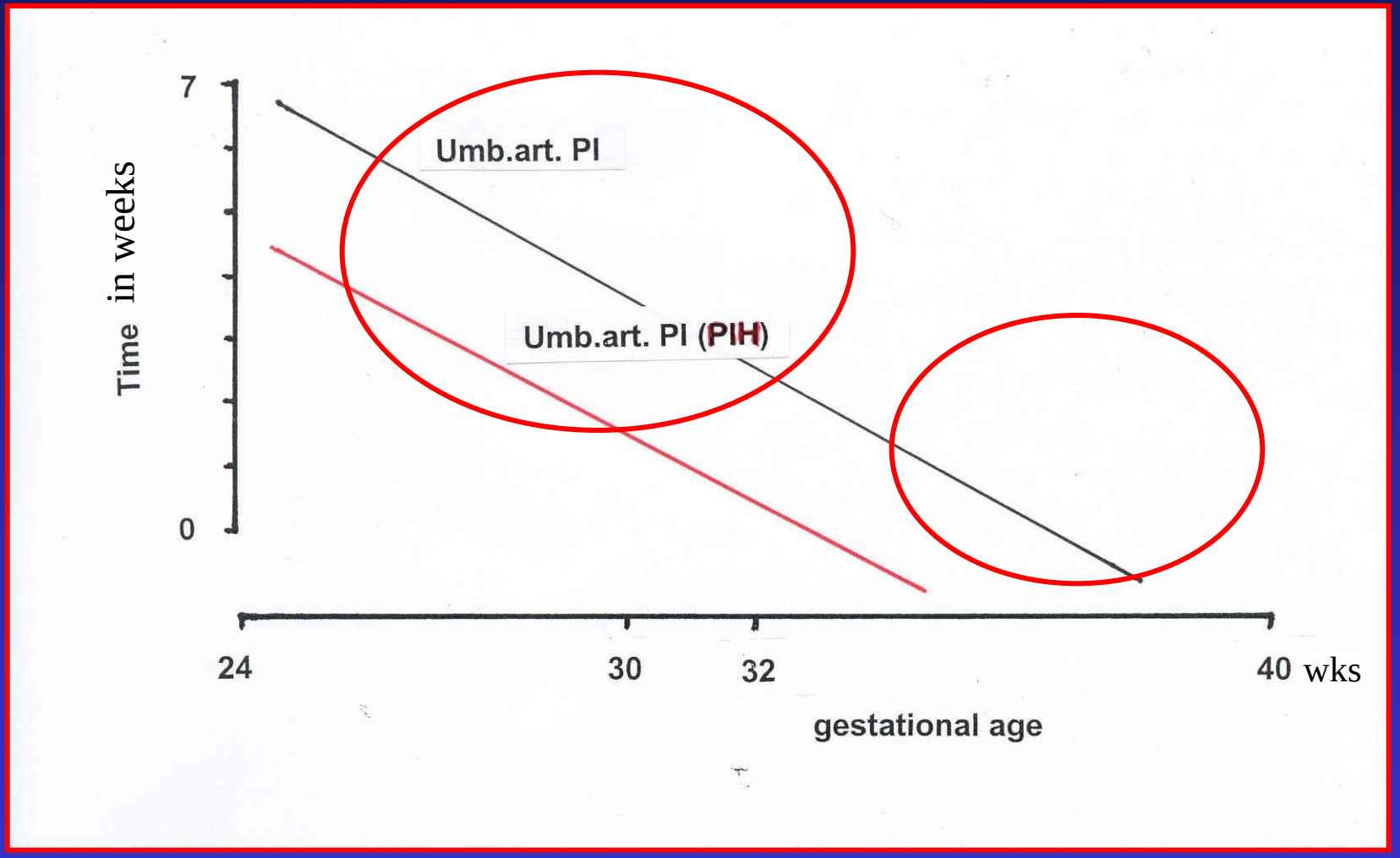
Moreover, IUGR is not accompanied by maternal hypertensive disease

Interval Doppler – FHR changes



(Arduini; Bekedam; Hecher; Pal)

Interval Doppler – FHR changes



(Arduini; Bekedam; Hecher; Pal)

Why does Doppler not work near term?

- Abnormal Dopplers in umbilical artery only occur in case of a 30-50% reduction of placental function/ capacity.

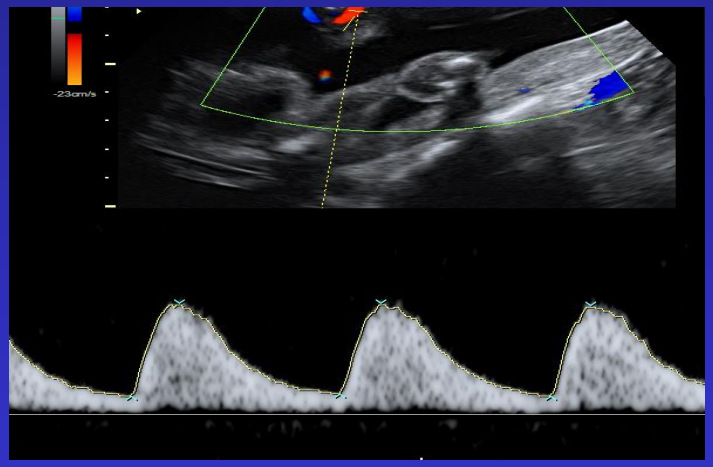
- Early in pregnancy the small fetus can live on ½ a placenta,

- Late in pregnancy the fetus cannot

Term IUGR/SFD

Many screening and diagnostic tests do not work properly

(and that holds especially for Doppler umbilical artery)

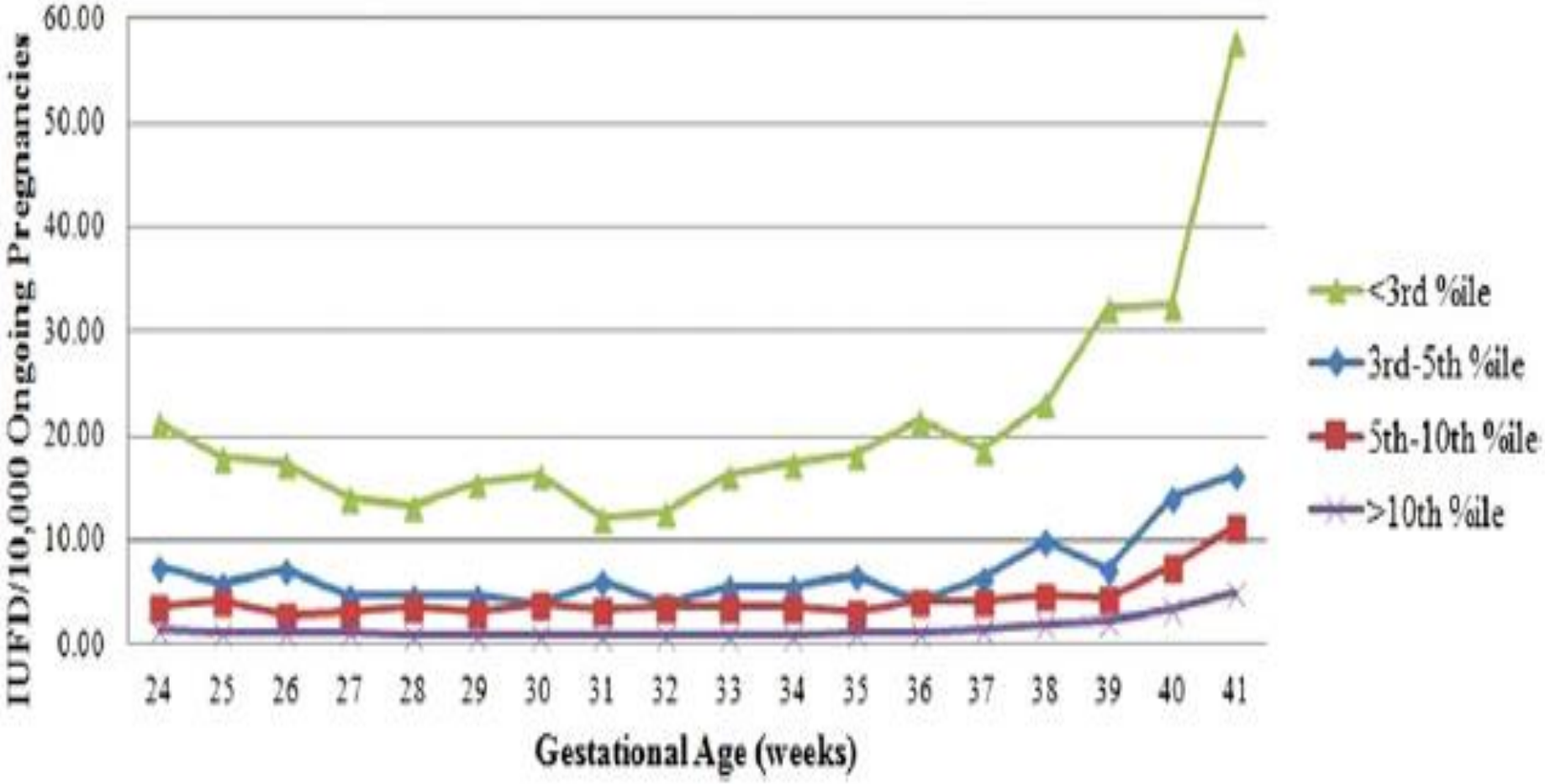


Moreover, most late IUGR are not small-for-dates

FIGURE

Risk of IUFD by gestational age

Nationwide data USA 2005



IUFD, intrauterine fetal death.

Pilliod. The risk of intrauterine fetal death in the SGA fetus. Am J Obstet Gynecol 2012.

Stillbirth, weight and gestational age

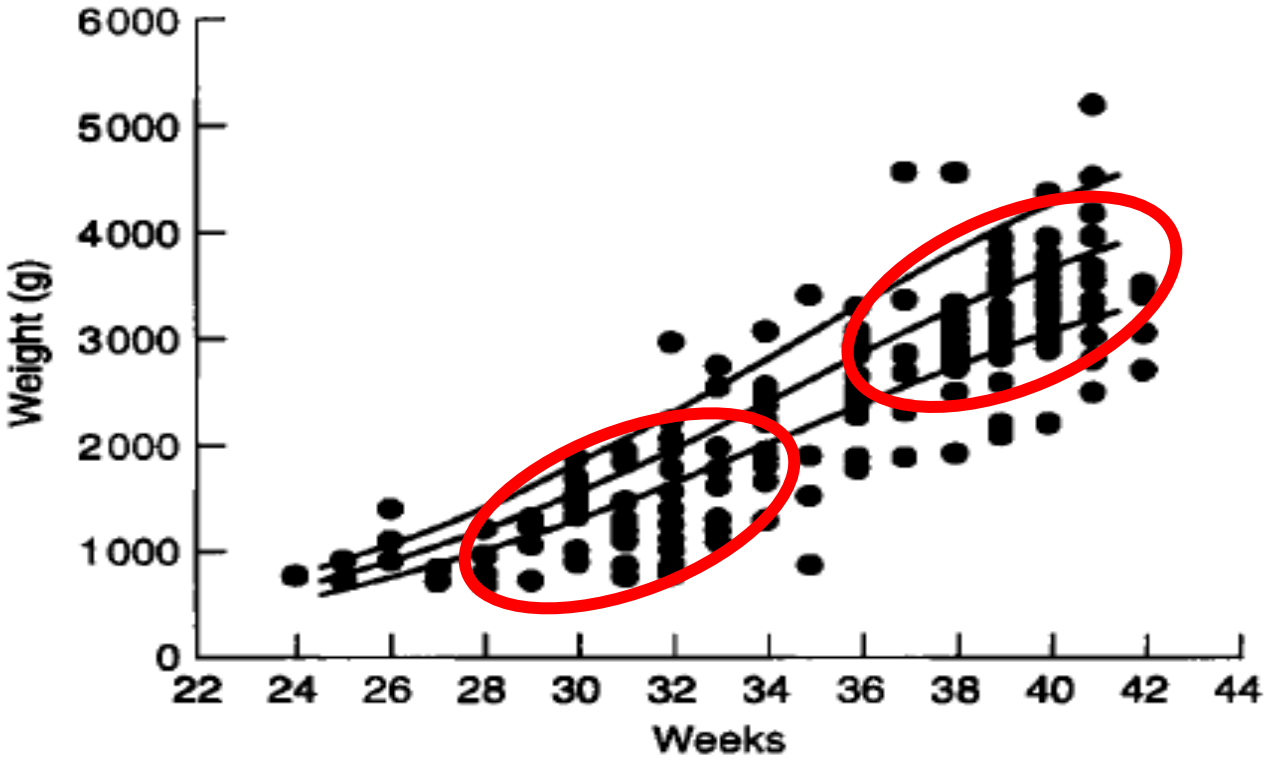
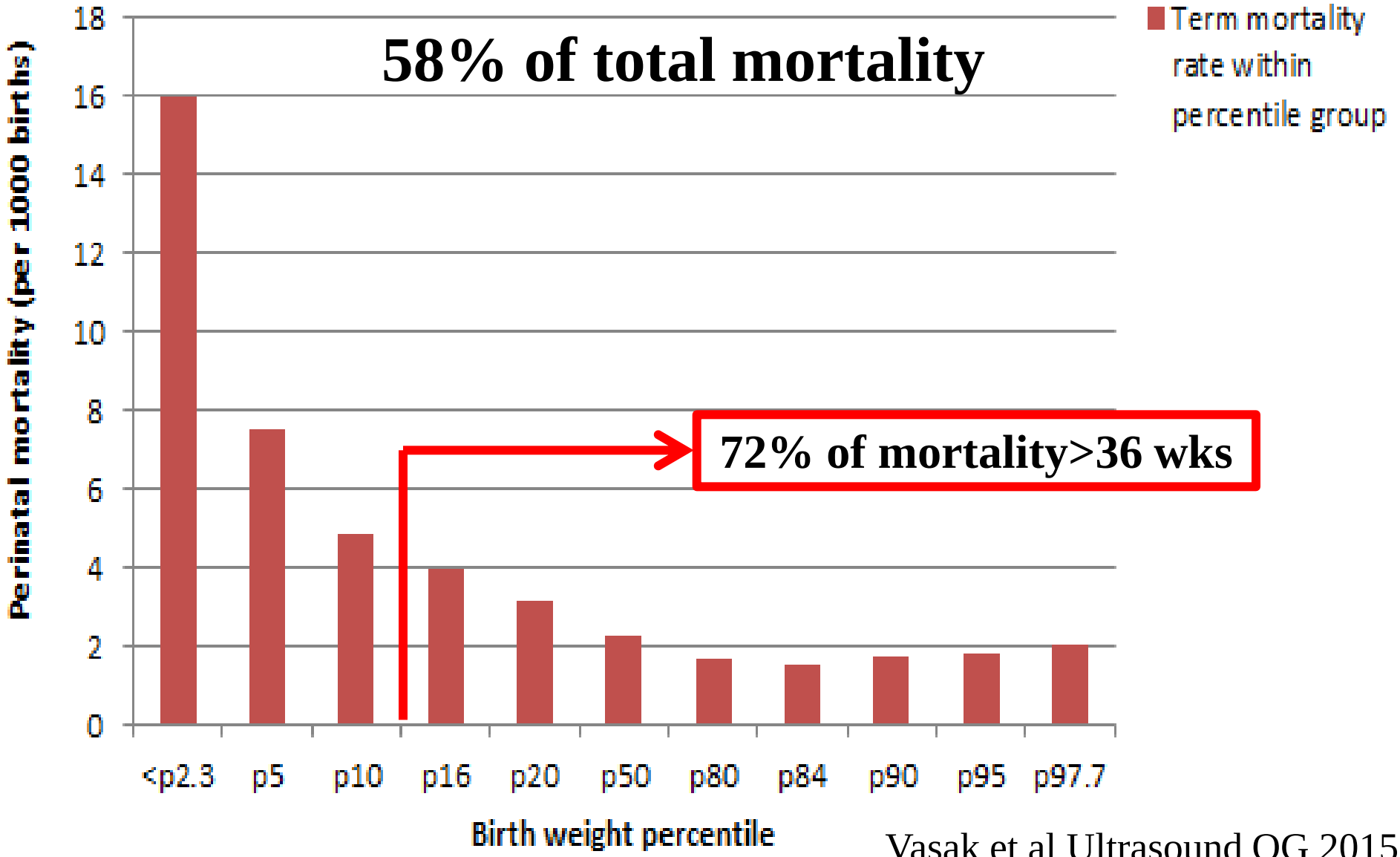


Fig. 2. Birthweights of 149 singleton, nonmalformed stillbirths in Trent Region in 1992, plotted against 10th, 50th and 90th centile lines of the local fetal weight standard. Gestational age based on ultrasound and adjusted for delay to delivery.

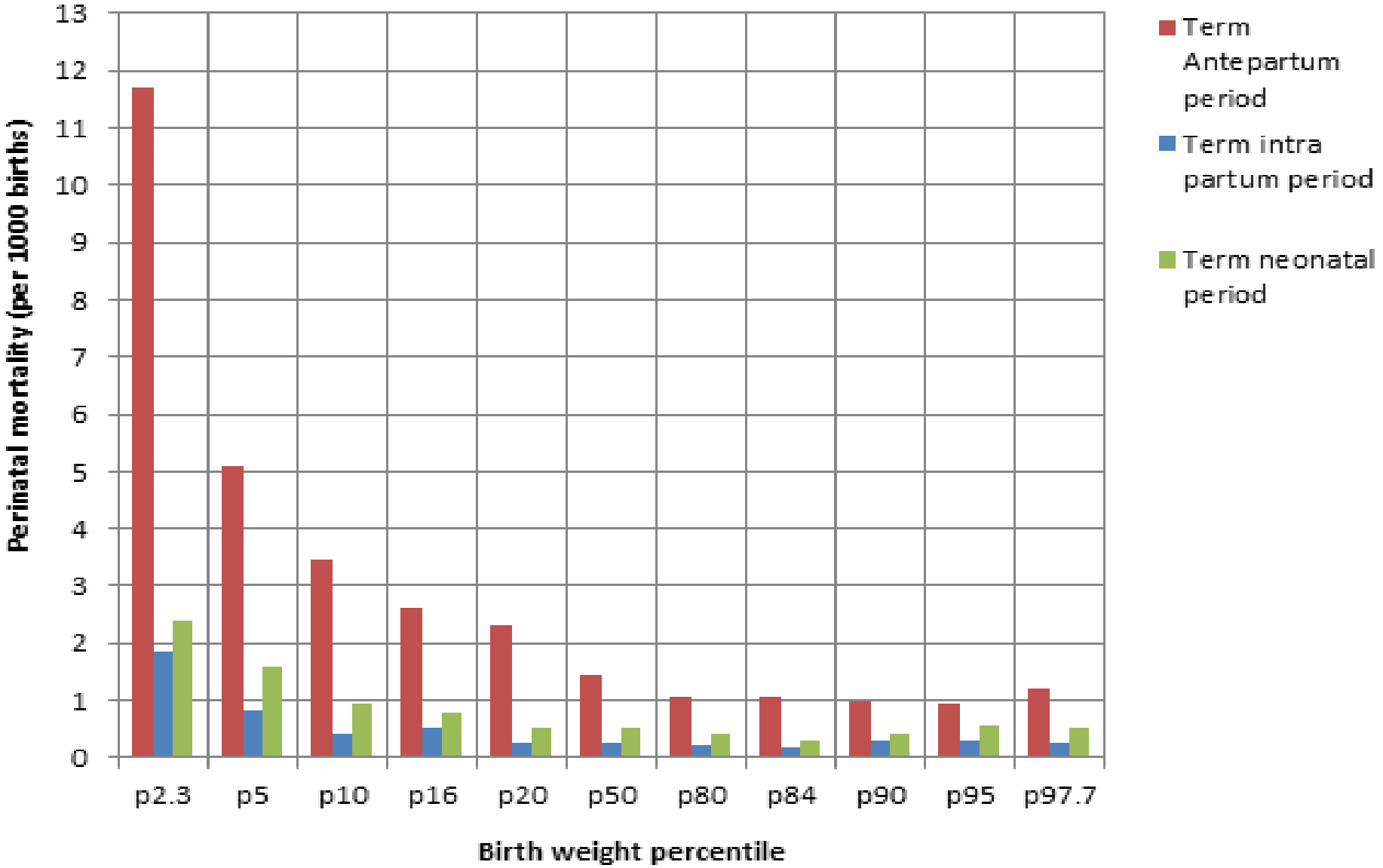
Gardosi et al, BJOG 1998; 45% weight< 10th centile

Perinatal mortality >+36 wks, Nlds 2000-2008

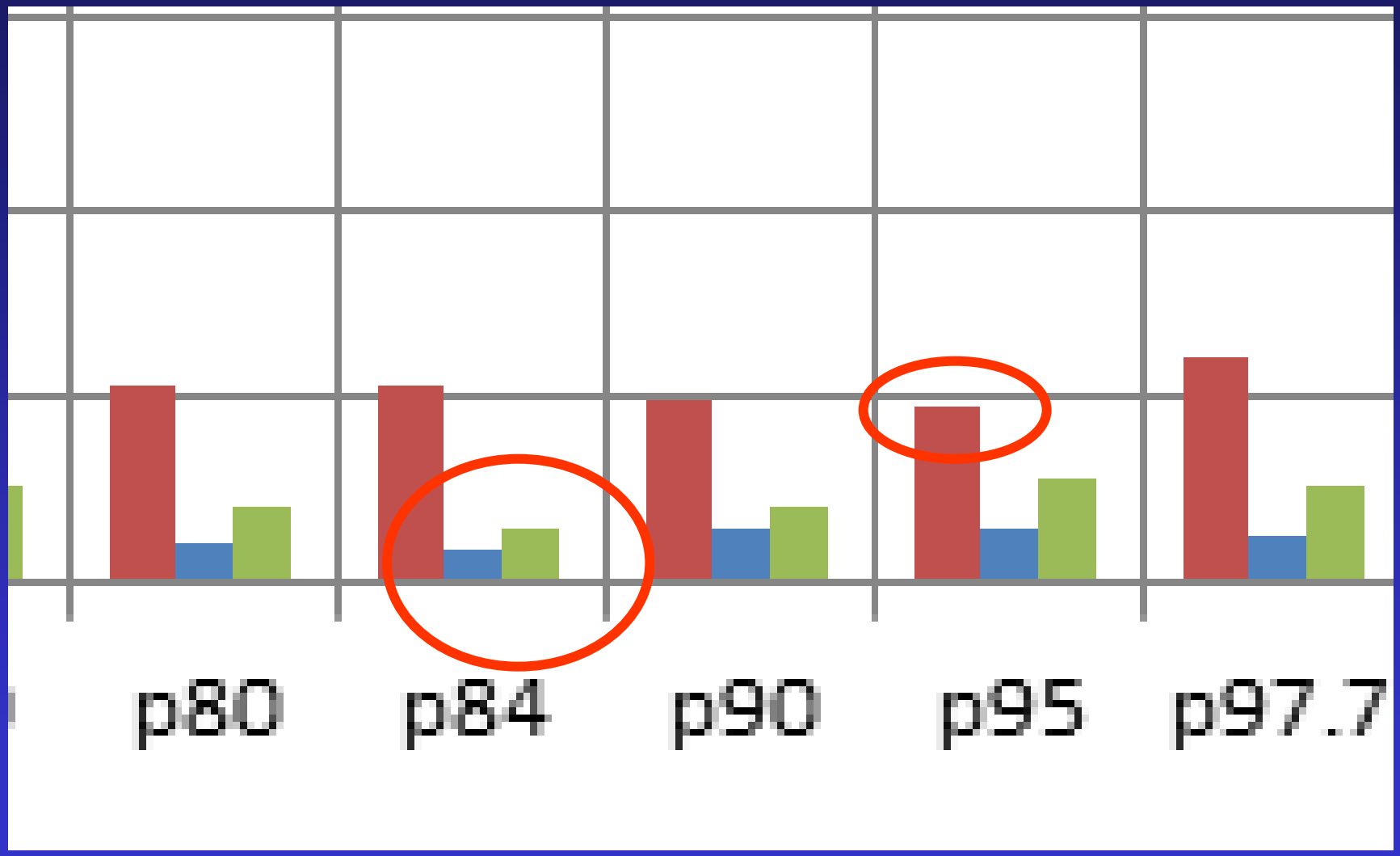


Vasak et al Ultrasound OG 2015

Perinatal mortality >= 36 wks



Perinatal mortality >= 36 wks



Antepartum stillbirth as compared to delivery related perinatal death at term, Scotland

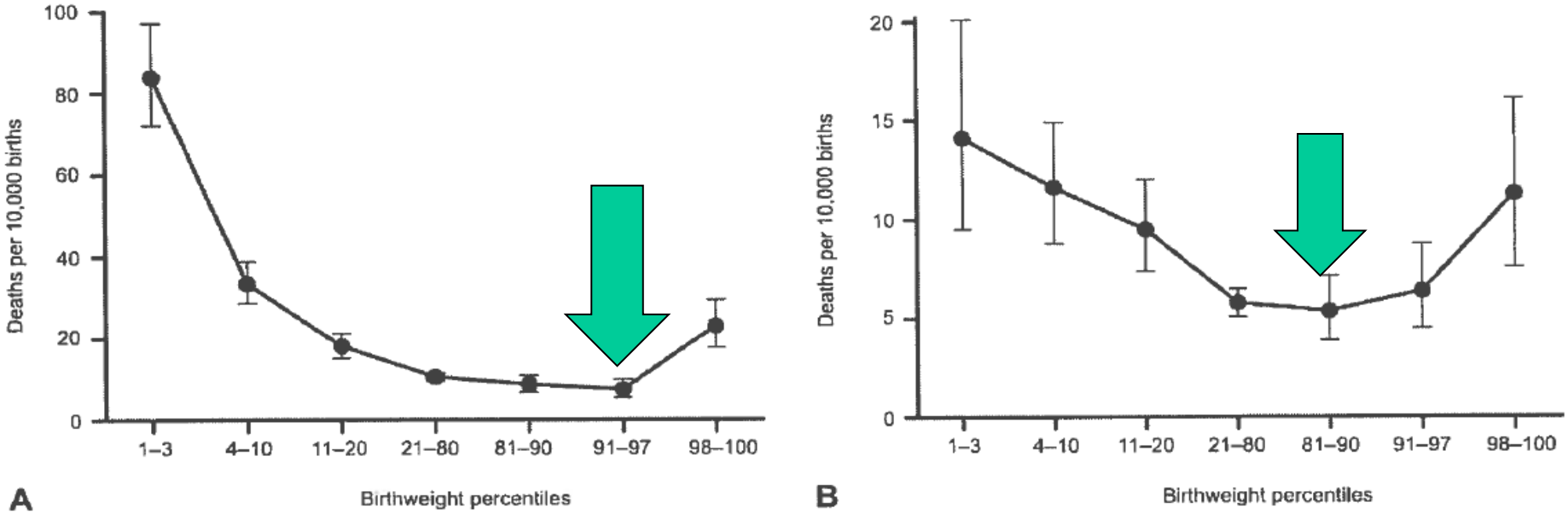
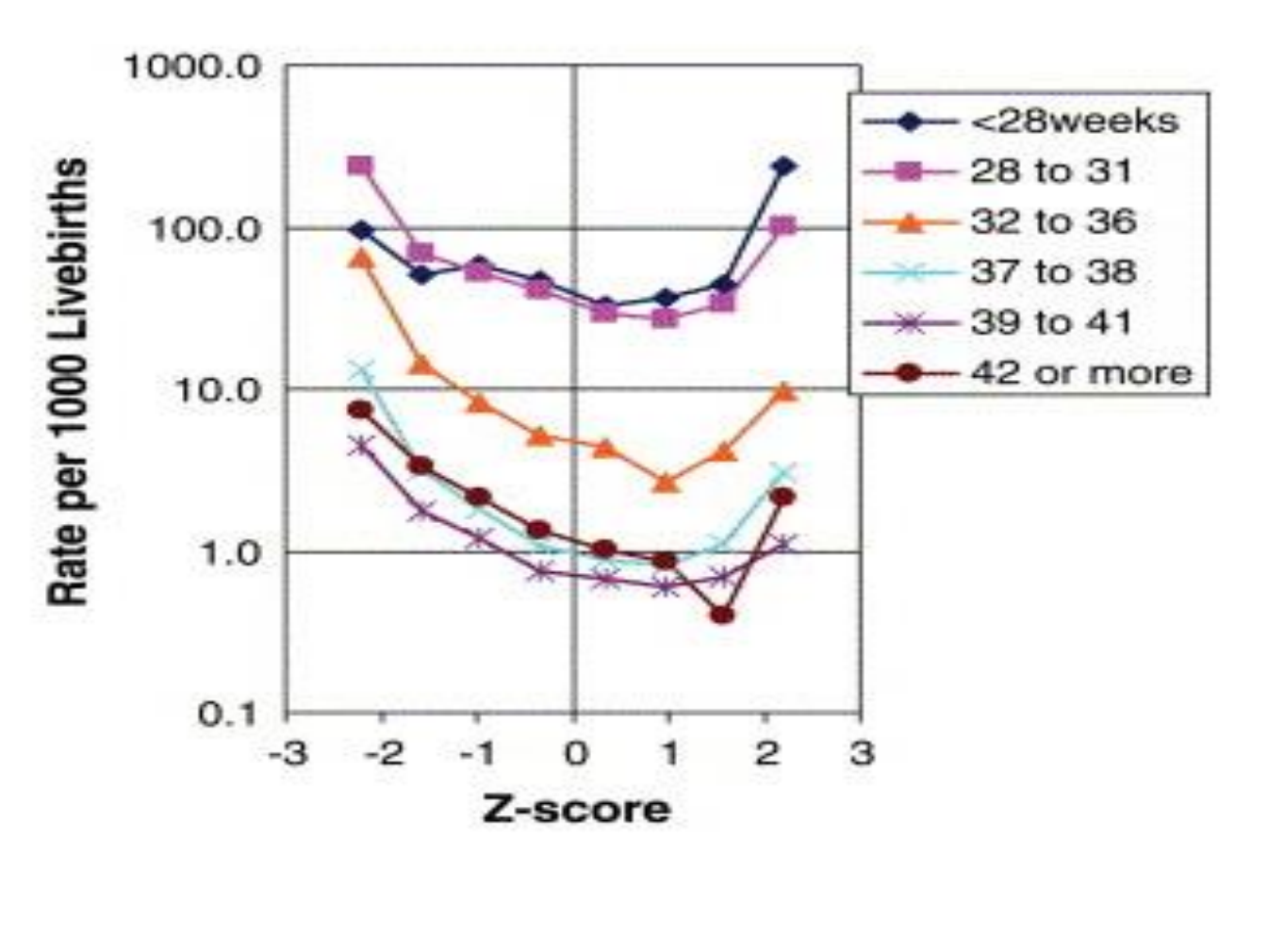


Fig. 1. Absolute risk per 10,000 pregnancies (95% binomial confidence intervals) of term perinatal death by birth weight percentile: **A.** antepartum stillbirth and **B.** delivery-related perinatal death (ie, intrapartum stillbirths and neonatal deaths).

Moraitis. Birth Weight Percentile and Perinatal Death at Term. Obstet Gynecol 2014.

Cerebral Palsy and birthweight centiles



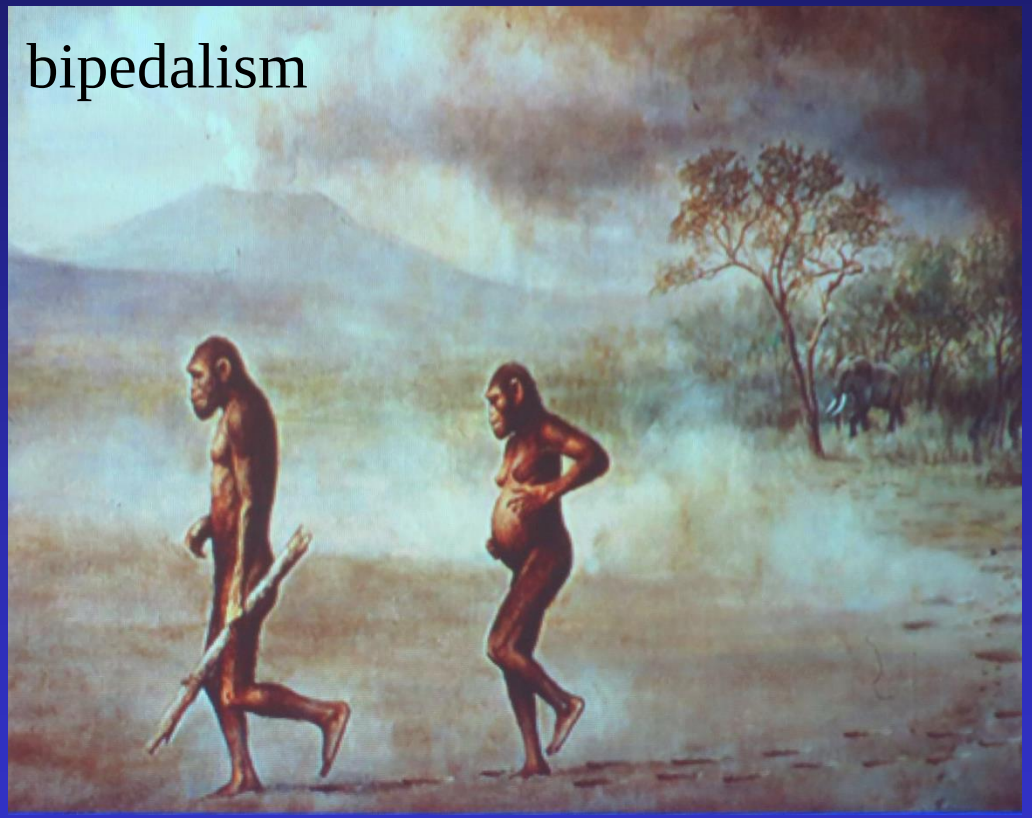
Yarvis et al, 2006

So, for short term survival

- Birth weight should be around the 90th centile
- ‘The bigger the better’
- Why are 90% of infants born too small?
- Or, why is…..

Or: why is human fetal growth restrained below optimal for fetal survival?

Large fetal head



constitute a major challenge for vaginal delivery*

*Trevathan et al, Evolutionary Medicine 189, 1999

Infant's death following maternal death

	RR infant death
Ethiopia; mat death<42d after delivery	46 (25.9-81.9)
Rural South Africa	15.2 (8.3-27.9)
Rural Tanzania, child death<10y:	5 40.7% versus 7.9%

Houle B et al; Finley JE et al; Moucheraud et al, Reprod. Health 2015

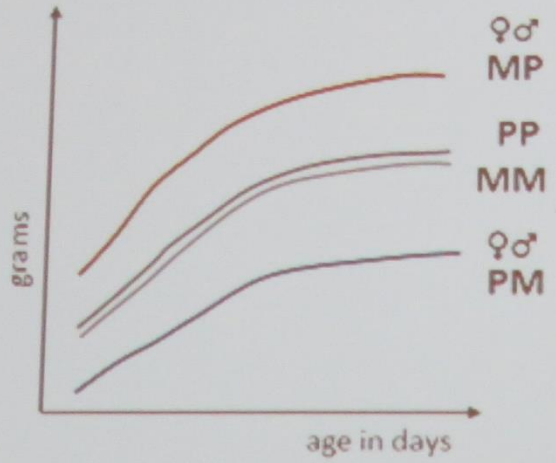
Mother versus father

The battle between the sexes

- Most paternally expressed genes enhance placental growth, while most maternally expressed genes reduce placental size (Tycko & Morison, 2002)
- Hydatidiform Mola: diploid set of sperm-only DNA, with all chromosomes having a sperm patterned methylation, results in overgrowth of the syncytiotrophoblast, in contrast to the dual-egg patterned methylation type (Paoloni-Giacobino 2007)

Mono versus polymyscus

The Mice



Class	Newborn weight (grams)
P P	1.63 ± 0.04
MM	1.62 ± 0.02
♀♂ PM	1.31 ± 0.02
♀♂ MP	2.17 ± 0.09

Dawson, W. D. (1965). "Fertility and Size Inheritance in a Peromyscus Species Cross." *Evolution*

So, for short term survival

- Birth weight should be around the 90th centile
- ‘The bigger the better’

But, what about long term outcome

Birth weight and death due to cardiovascular disease <65 y of age

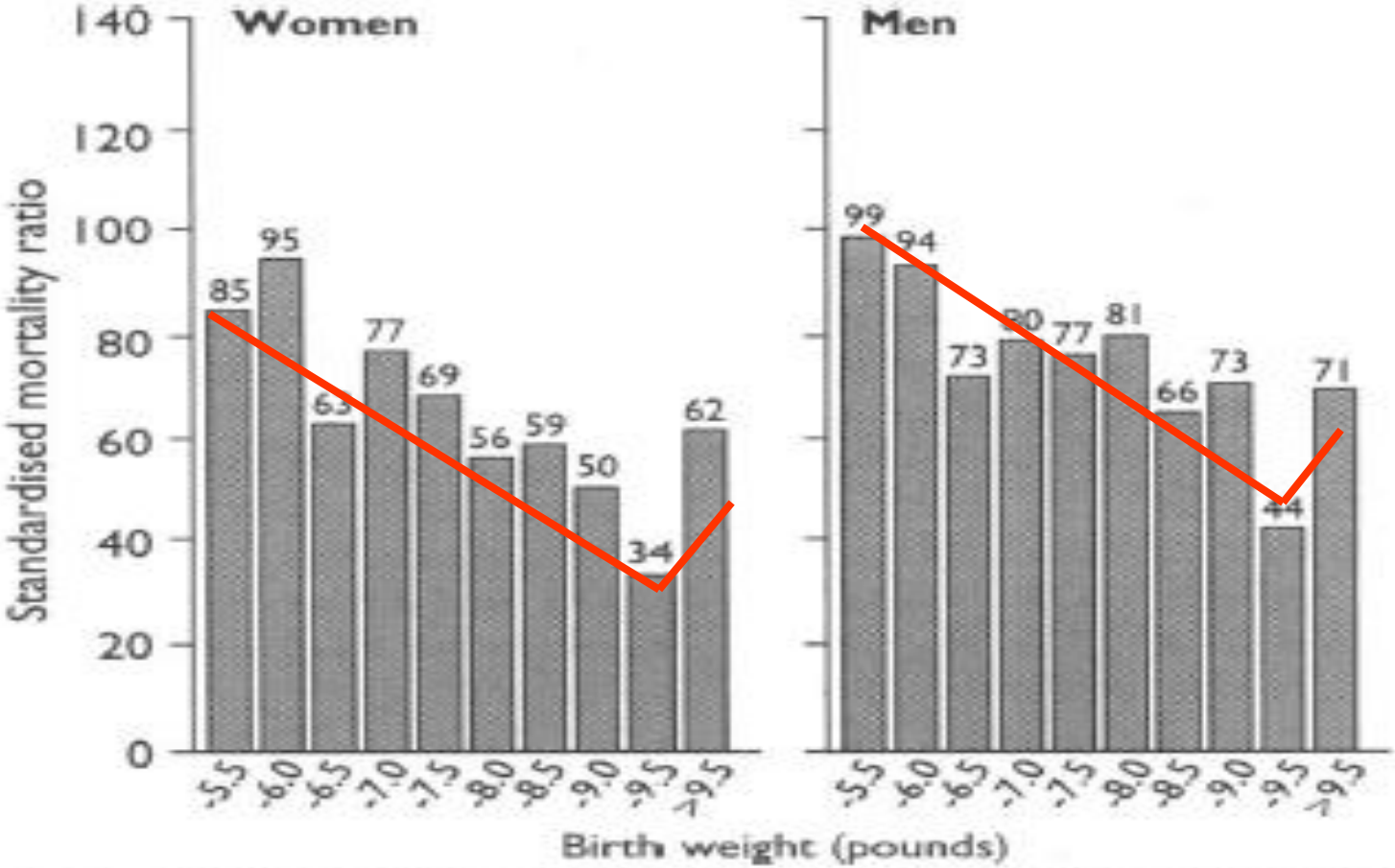


FIG 1—*Standardised mortality ratios for cardiovascular disease below age of 65 according to birth weight*

Osmond et al, BMJ 1993

Chronic Heart Disease and Stroke in relation to birth weight

TABLE 2. Rates of CHD and Stroke by Birth-Weight Category Distribution

	Rate per 10 000 (95% CI) by Birth-Weight Category					
	<3250 g (n=4052)	3250–3749 g (n=5305)	3750–4249 g (n=1199)	≥4250 g (n=247)	Sex-Adjusted HR (95% CI) per kg (n=10 803)	HR (95% CI) per Birth Weight for Sex and Gestational Age *z* Score (n=9700)
CHD	15.0 (12.7–17.9)	11.9 (10.1–14.2)	7.2 (4.6–11.6)	7.4 (2.8–26.2)	0.63 (0.51–0.78) *P*<0.001	0.83 (0.73–0.94) *P*=0.004
Stroke	7.0 (5.5–9.1)	3.2 (2.4–4.5)	1.9 (0.8–5.6)	1.8 (0.26–13.0)	0.41 (0.29–0.59) *P*<0.001	0.74 (0.60–0.92) *P*=0.007
CHD or stroke	21.1 (18.3–24.4)	14.9 (12.8–17.3)	9.0 (6.2–13.8)	9.2 (3.9–27.3)	0.57 (0.47–0.69) *P*<0.001	0.81 (0.73–0.91) *P*<0.001

n=10 803.

Lawlor et al, Circulation 2005

So, for short and long term survival

- Birth weight should be around the 90th centile
- Why?

So, for short and long term survival

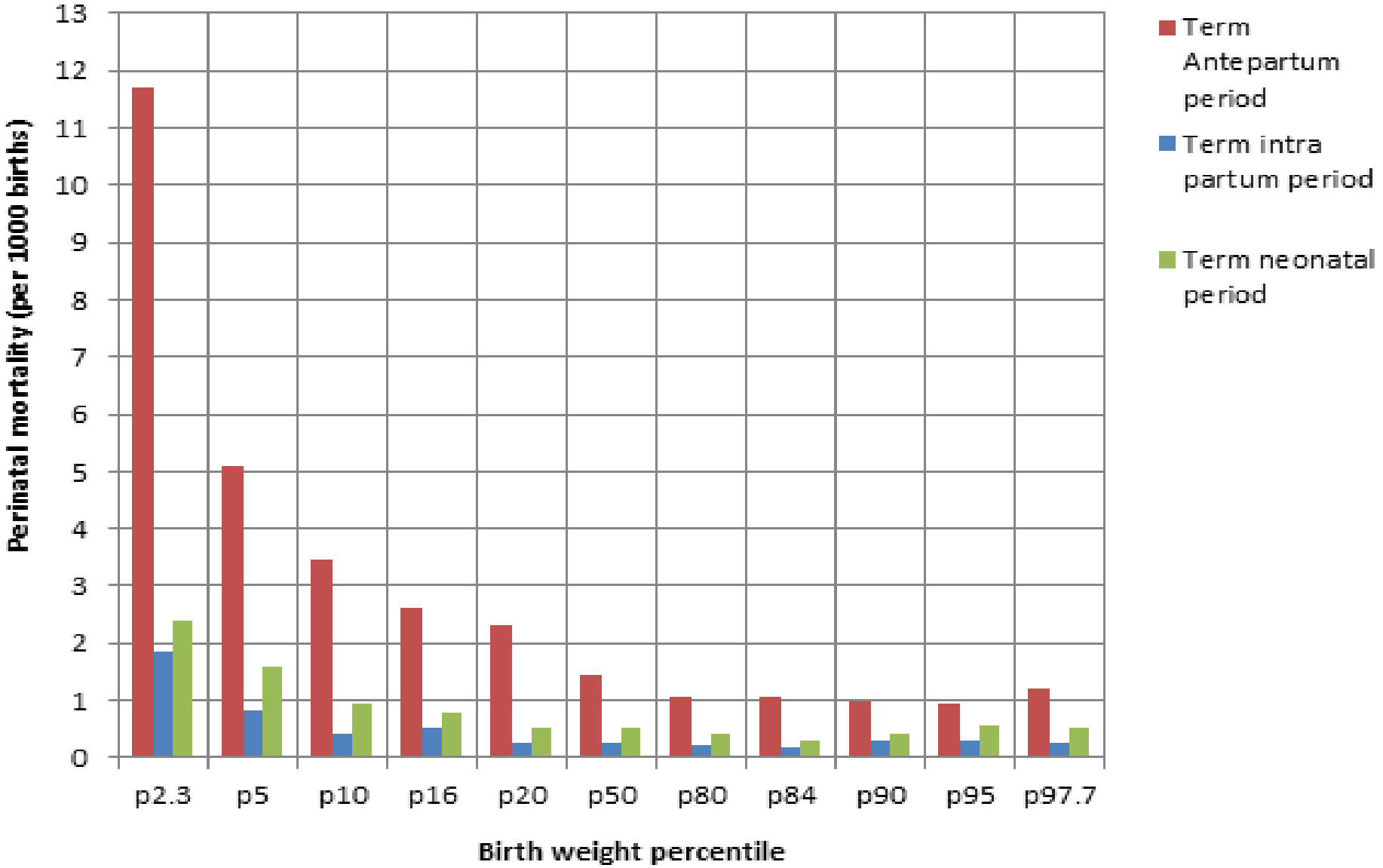
- Birth weight should be around the 90th centile
- Why?
- Because these infants had an optimal intrauterine growth, without any growth restraint

(interim) Conclusion

- So, it is not only the very small ones that are at increased risk
- In fact, most IUDs occur in fetuses with a weight in the so-called normal range
- Which makes identification even more difficult

- So, it is time for an integrated risk assessment, including trends in fetal weight estimates, signs of blood flow redistribution and maternal characteristics

Perinatal mortality >= 36 wks



Incidence of fetal growth restriction (abnormal CP ratio) according to birth weight centiles

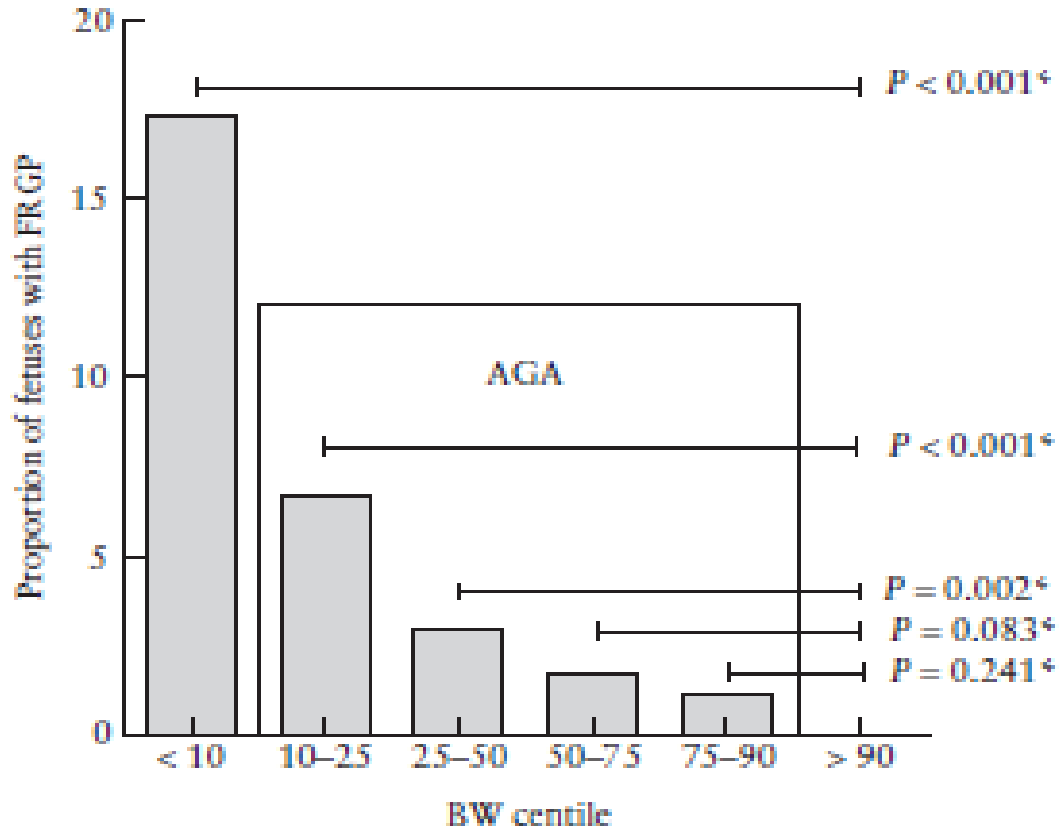


Figure 3 Percentage of term fetuses with failure to reach growth potential (FRGP) according to their birth weight (BW) centile group (i.e. percentage of fetuses presenting a cerebroplacental ratio (CPR) multiple of the median (MoM) value below the established FRGP normality threshold (CPR MoM = 0.6765), calculated after subtracting those cases with CPR MoM < 5th centile observed in the group with BW > 90th centile). Appropriate-for-gestational-age (AGA) fetuses present a progressive decrease of CPR, which is especially important in the group with BW < 25th centile.
*Chi-square test plus Holm's correction for multiple comparisons.

Morales-Rosello et al, UOG 2014

CS and acidosis according to redistribution or not

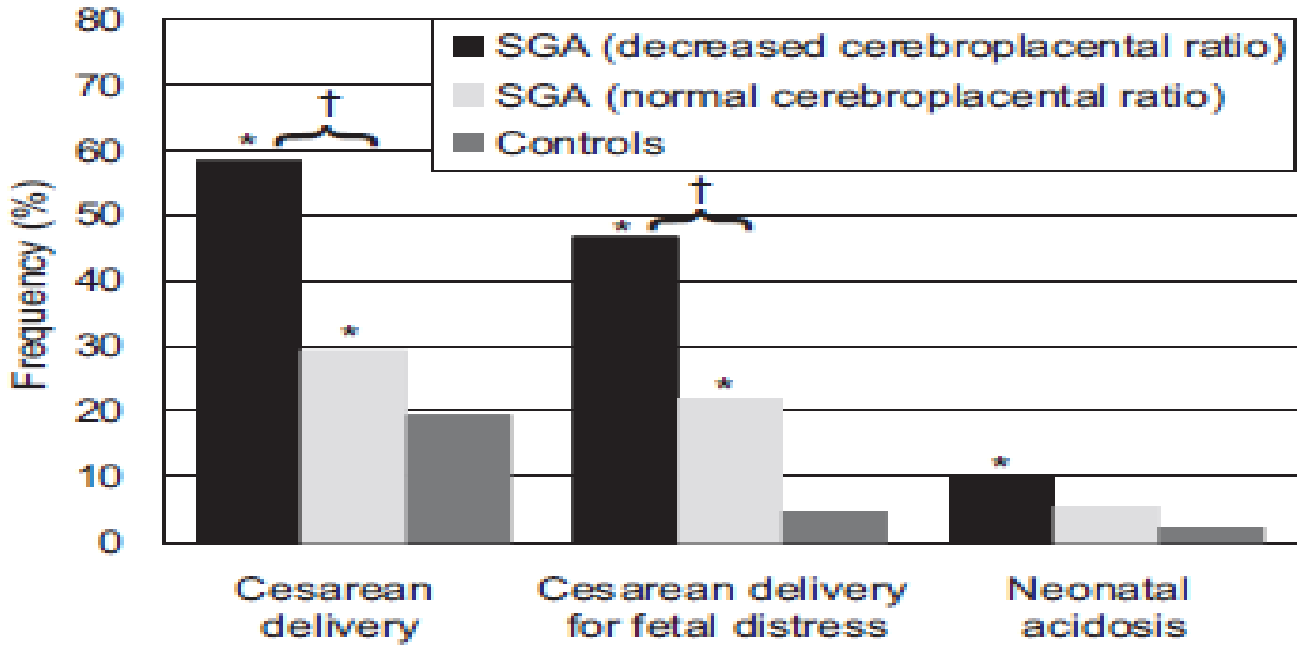


Fig. 2. Frequency of intrapartum cesarean delivery, emergency cesarean for nonreassuring fetal status, and neonatal acidosis in controls and small-for-gestational age (SGA) fetuses with and without decreased cerebroplacental ratio. *$P<.05$ with control participants the reference group; †$P<.01$ among SGA cases.

Cruz-Martínez. Brain Doppler and Fetal Status in Small-for-

The term fetus at risk

Redistribution as a proxie for placental impairment?

CPR at 36 wks, and birth weight Z score and C.sections for fetal distress;

(Akolekar et al, Ultras O&G, 2015; screening of >6.000 singletons)

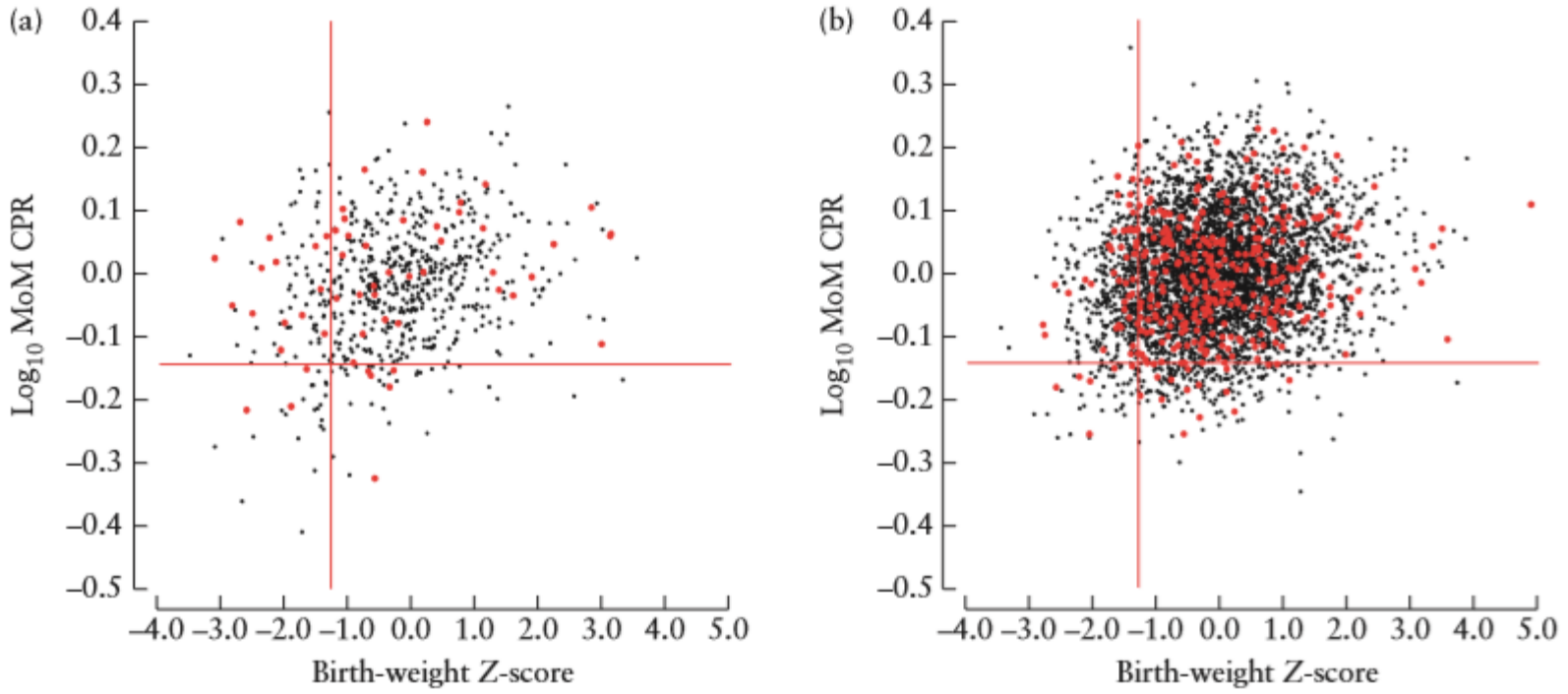


Figure 3 Relationship between log_{10} multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight Z-score in pregnancies delivering by Cesarean section for fetal distress (●) and those delivering vaginally (●) ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red line corresponds to 10th percentile for birth weight and horizontal red line corresponds to 5th percentile for CPR.

Prediction of IUGR and adverse outcome by feto-placental Doppler at 37 wks

Stefania Triunfo…..Fransesc Figueras, Palermo April 15, 2016

- Low risk cohort of 1000 women
- Measured everything at 37 wks
- Adverse Outcome: 35 in AGA, 5 in SGA & 6 in FGR

- Prediction of Adverse Outcome: 29% for 10%FPR
- (EFW centile+CRP+UVBF, +Ut-API?)

42 SFD monitored longitudinally

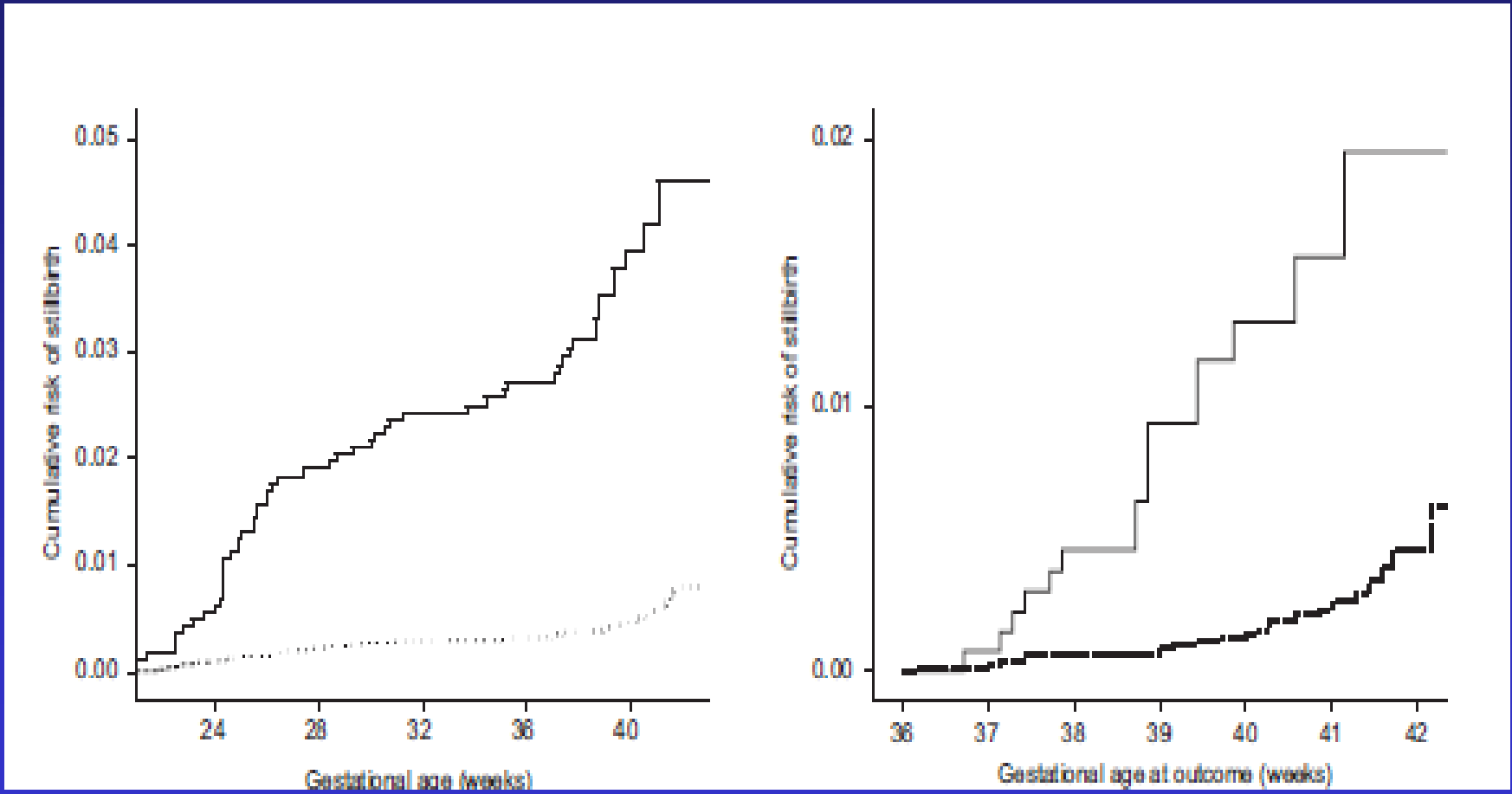
- CPR at intake (34-36wks) no prediction of composite morbidity
- However, change from normal to abnormal showed some correlation

(Vasak et al, in prep)

Biophysical screening tests

- Early identification is essential
  - Customized growth charts
  - Doppler uterine artery?
  - Umbilical/MCA Doppler ratio
  - Serial fetal growth measurements?
  - Measure of autonomic FHR control
  - Fetal movements !
  - Unlikely to be useful: serial AF assessment, FHR monitoring

Cumulative stillbirth risk according to ut artery PI at 19-23 wks



Singh et al, O & G, 2012

Risk factors for 3rd trimester stillbirth

	OR multivariate
• IUGR/SFD	7.0 (3.3-15.1)
• Age>35	4.1 (1.0-16.5)
• BMI>25	4.7 (1.7-10.2)
• Education<10 y	3.4 (1.2-9.6)
• IUGR/BMI>25	71 (14-350) univariate OR

Froen, Gardosi et al, 2004 ; 76 SIUD, 582 controls

In this context, it is good to know, that…

- The risk of a term IUFD in a nulliparous 36 years old woman is greater than the risk of her having a child with a chromosomal anomaly

Fretts and Duro, 2008

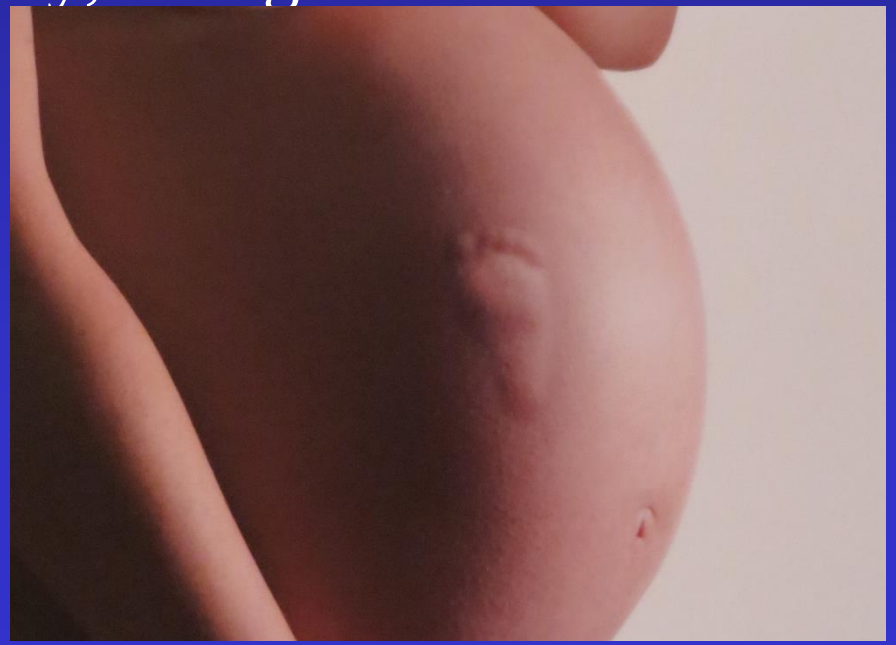
Risk factors for stillbirth;

multivariable analysis (Gardosi et al, 2013)

	Adjusted RR
• Parity 0	1.8 (1.3-2.5)
• African/Indian/Pakistani	2.3-3.0
• BMI>35	1.6 (1.1-2.4)
• Pre-existing diabetes	3.9 (1.7-8.9)
• Antepartum haemorrhage	3.4 (2.6-4.5)
• Active smoker no FGR	2.5 (1.7-3.6)
• Active smoker FGR	5.7 (3.6-8.9)
• Non-smoker FGR	7.8 (5.6-10.9)

Structured information on fetal movements at 18 wks

- More than 50% reduction in IUFD in nulliparous women (OR 0.36, 95%CI 0.19-0.69)
- No change in multiparous women, smokers, obese women, maternal age >34 y, foreigners

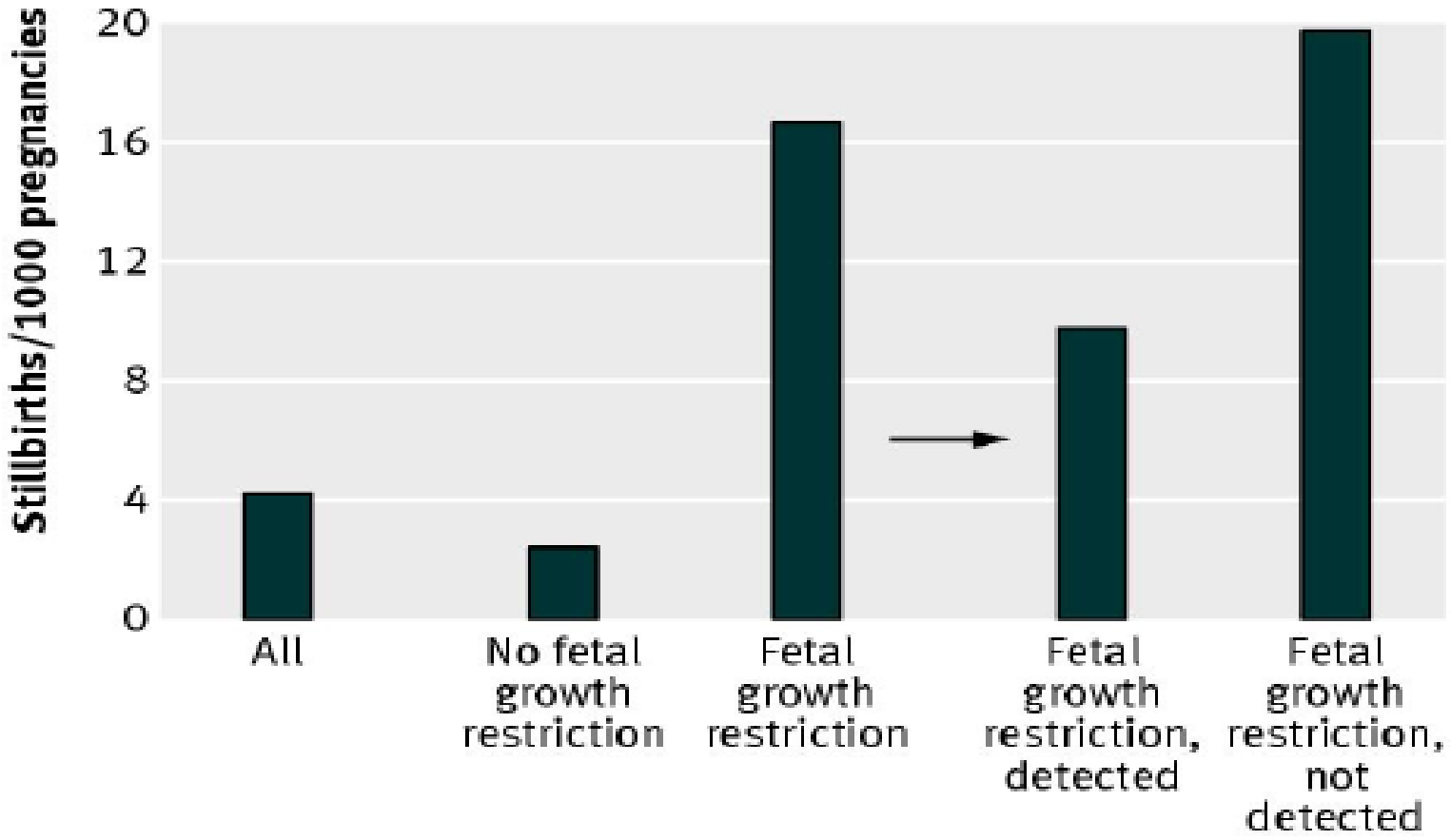


Saastad e.s. BMC Research notes, 2010,3:2

IUGR contingency screening

- **Combined screening at 11-13 wks**
- (history, MAP, UtPI, PLGF,PAPP-A)
- High Risk (20%) Low Risk (80%)
- Aspirin
- **Combined screening at 22 wks**
- (UtPI, Umb aPI, MAP, serum PLGF/sFLT-1)
- High Risk (…%) Moderate Risk (…%) Low Risk (…%)
- See every 2 wks
- **Combined screening at 32 weeks**
- (UtPI, MAP, serum PlGF ,ultras customised fetal weight)
- High Risk (…%) Low Risk (…%)
- See every 1 wk: fetal growth velocity, CPR nothing else

Stillbirth rate in relation to FGR



Gardosi et al, BMJ 2013; population based study, 389 stillbirths>24 wks (0.42%)

Mid and 3rd trimester screening for SGA

- Screening at 19-23 wks, using mat factors, fetal biometry, UtA PI, PlGF and AFP :

  Detection rate SGA< 5th centile for 10% FPR:

<32 wks	32-36	>36wks
88%	66%	43%

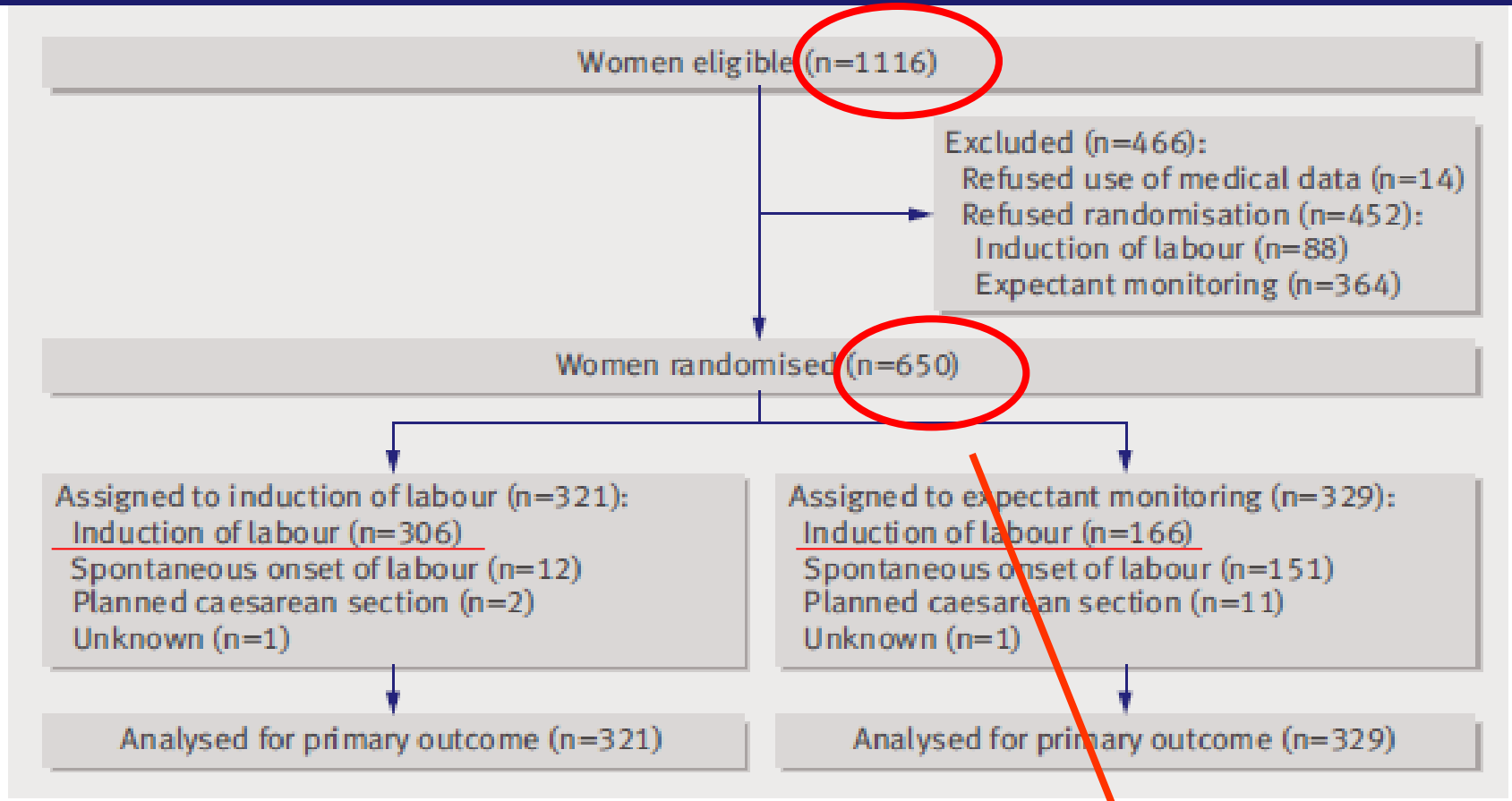
- Screening at 30-34 wks, using mat factors, EFW, UtA PI, MAP, PlGF

  Detection rate SGA < 5th centile for 10% FPR:

94%	65%

Poon et al and Bakalis et al, Ultrasound O&G 2015

DIGITAT study



Flow diagram of the trial process

BMJ | ONLINE FIRST | bmj.com

Broers et al, 2010

Perinatal mortality: 0

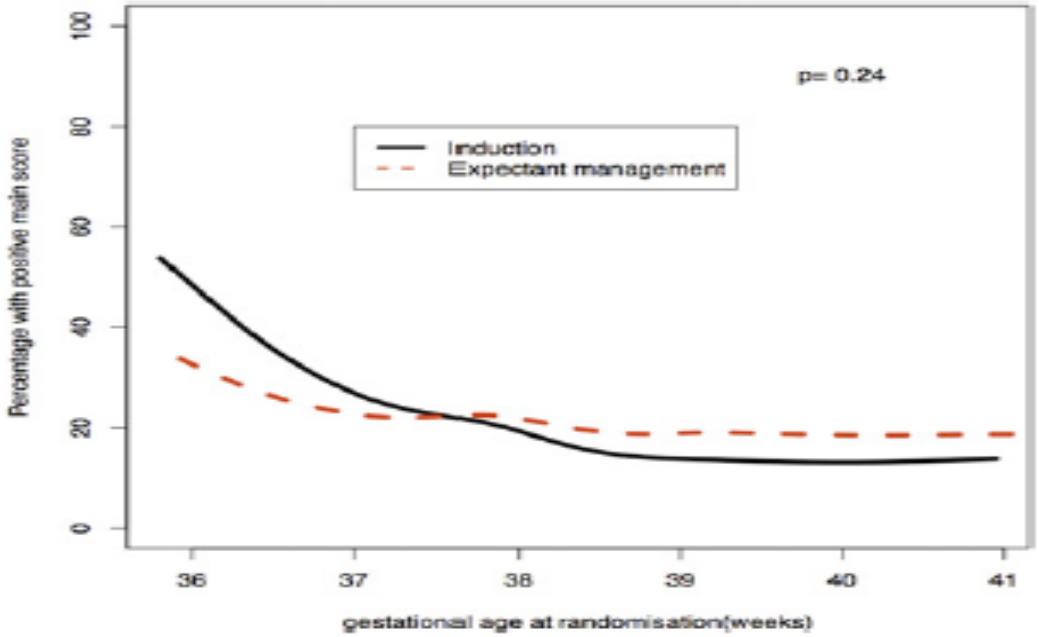
DIGITAT study

	Induction	Expect man
N	321	329
CS	14 %	13.7%
Birthweight<3rd cent	12.5%	30.6%
Birthweight>25th c	7.2%	6.1%
PNMortality	-	-
Composite Morbidity	5.3%	6.1%

Boers et al BMJ 2010;341;c7087

FIGURE 4

Gestational age at randomization vs percentage of neonates with a positive MAIN score



MAIN, Morbidity Assessment Index for Newborns.

Boers. Neonatal morbidity in the disproportionate intrauterine growth intervention trial at term. Am J Obstet Gynecol 2012.

Timing of delivery of the IUGR/SGA fetus

• < 26 wks	Refrain from intervention
• 26-30 wks	Abn DV and/or STV/decelerations
• 30-32 wks	same or reversed EDV umb a
• 32-34 wks	same or absent EDV umb a
• 34-37 wks	same or abn umb a PI
• >37 wks	same or EFW<3rd c,CPR>95th c
• >38+ wks	same or EFW< 10th centile

Adapted from Figueras & Gratacos, 2014

So,……

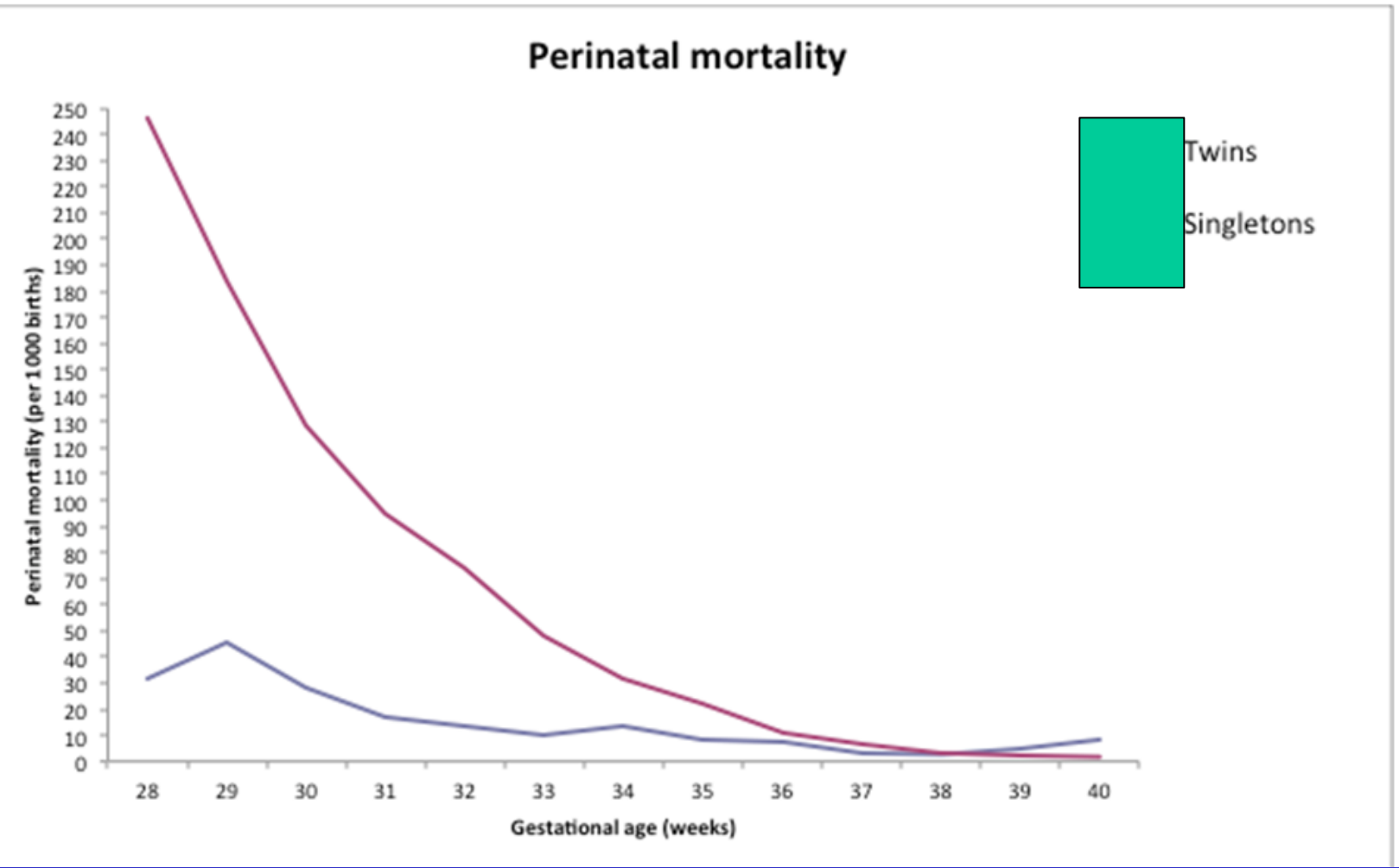
- These are exciting times for all those studying late IUGR
- Diagnosis of SGA is insufficient
- Diagnosis of true (late) IUGR remains difficult
- Assessment may include:
- - monitoring trends in fetal growth
  - Ut artery
  - CP ratio
- What will be the timing of the scan(s)?
- Finally, be aware of false positives and unnecessary interventions

“ I am a fetus in the womb
I fear it may become my tomb
if only I could give a shout
to get my doctor to get me
out!”

a British Medical Student

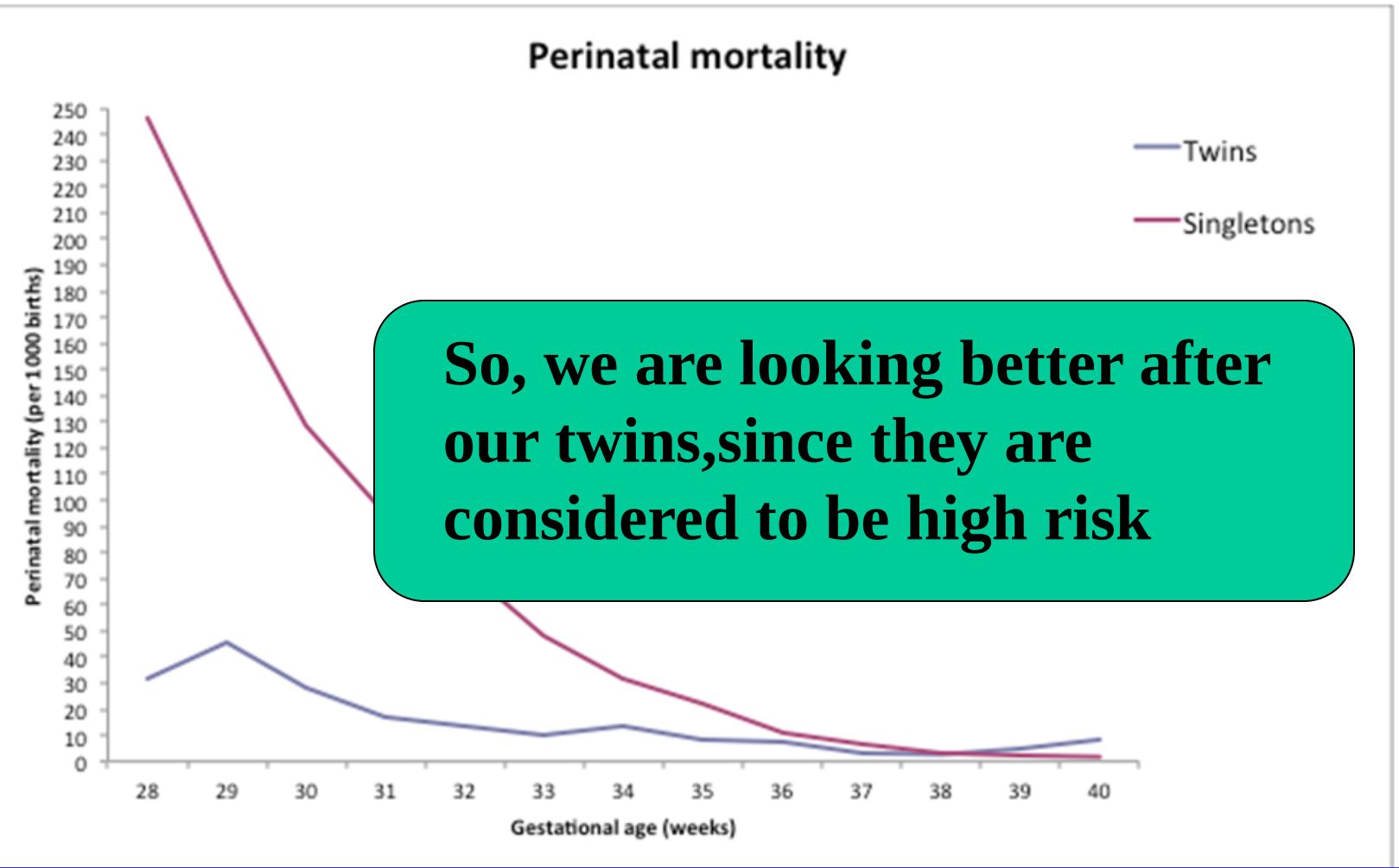
Thank you

Perinatal mortality singletons vs twins



Vasak et al, AJOG in press

Perinatal mortality singletons vs twins



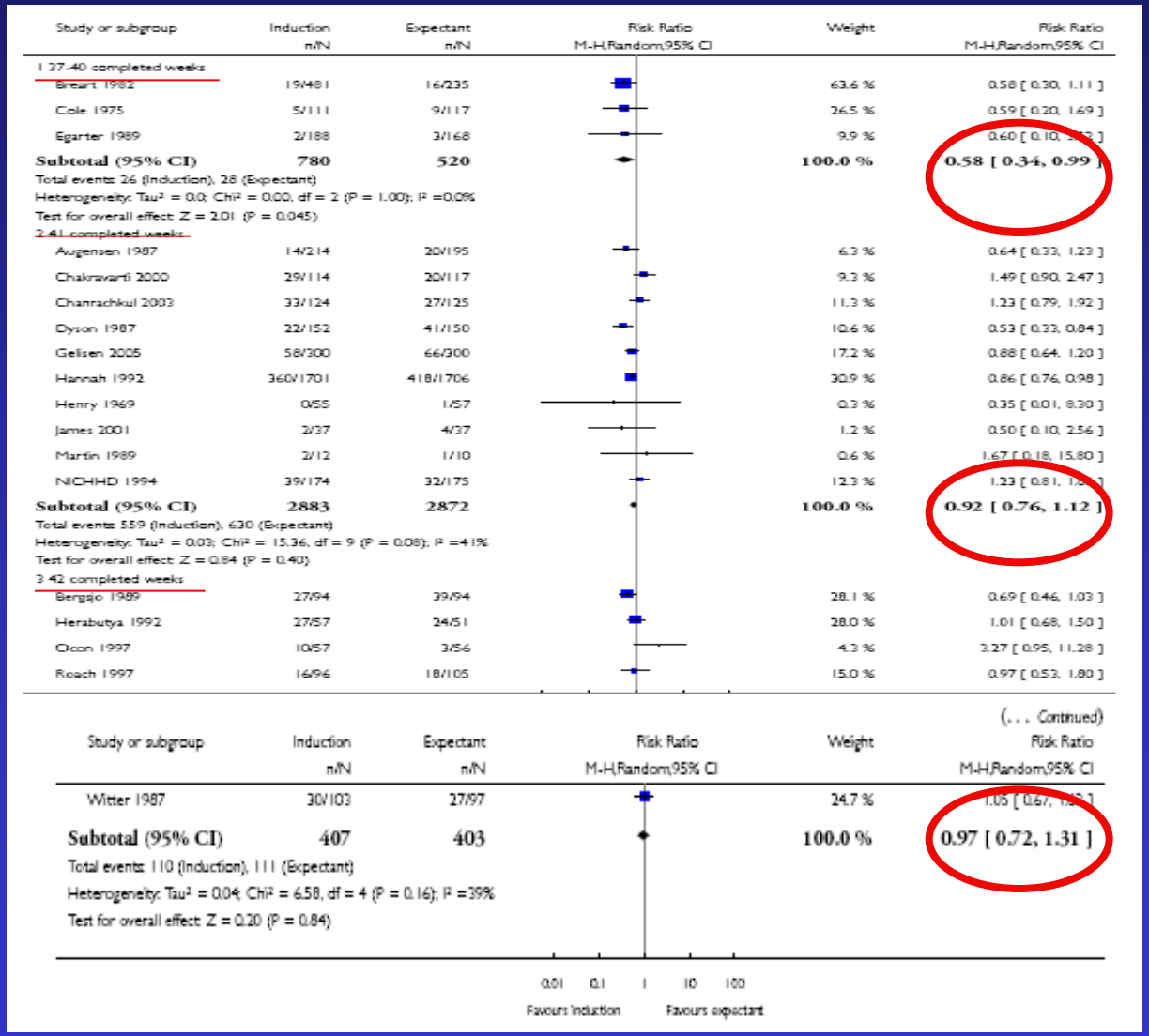
Vasak et al, AJOG in press

Cochrane: induction vs expectant management

37-40 wks

>41 wks

> 42 wks



Magnitude of fetal death;

singletons without cong malformations

Author	country (y)	population	stillbirths	%
Pilliod	USA 2005	3.400k	13.829	0.4%
Vasak	NL 2000-8	1.200k	5.048	0.35% (>28wks)
Gardosi	UK 2011	92k	389	0.42%

Magnitude of fetal death;

singletons without cong malformations

- Author country (y) population stillbirths %

- Pilliod USA 2005 3.400k 13.829 0.4%
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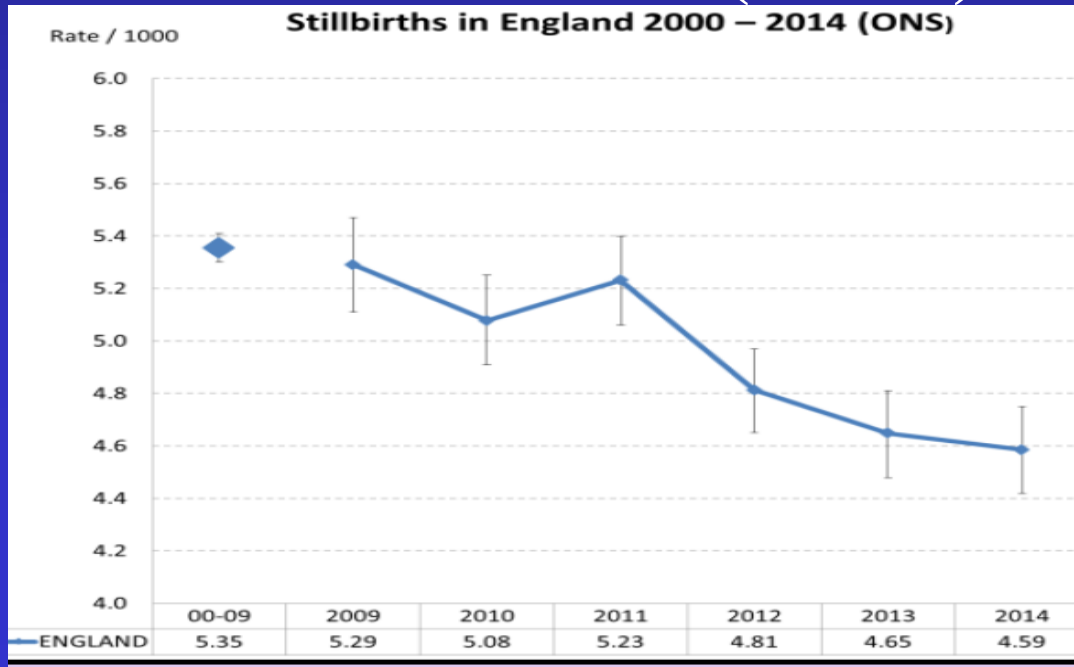
- Gardosi UK 2011



Perinatal News, Autumn 2015

Magnitude of fetal death;

singletons without cong malformations

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Pilliod	USA 2005	3.400k	13.829	0.4%
Vasak	NL 2000-8	1.170k	4.119	0.35% (>28wks)
Gardosi	UK 2011	92k	389	0.42%

Newcastle upon Tyne (>28 wks):

1961-1980	2.34%
1981-2000	0.47%

Glinianaia et al, 2010

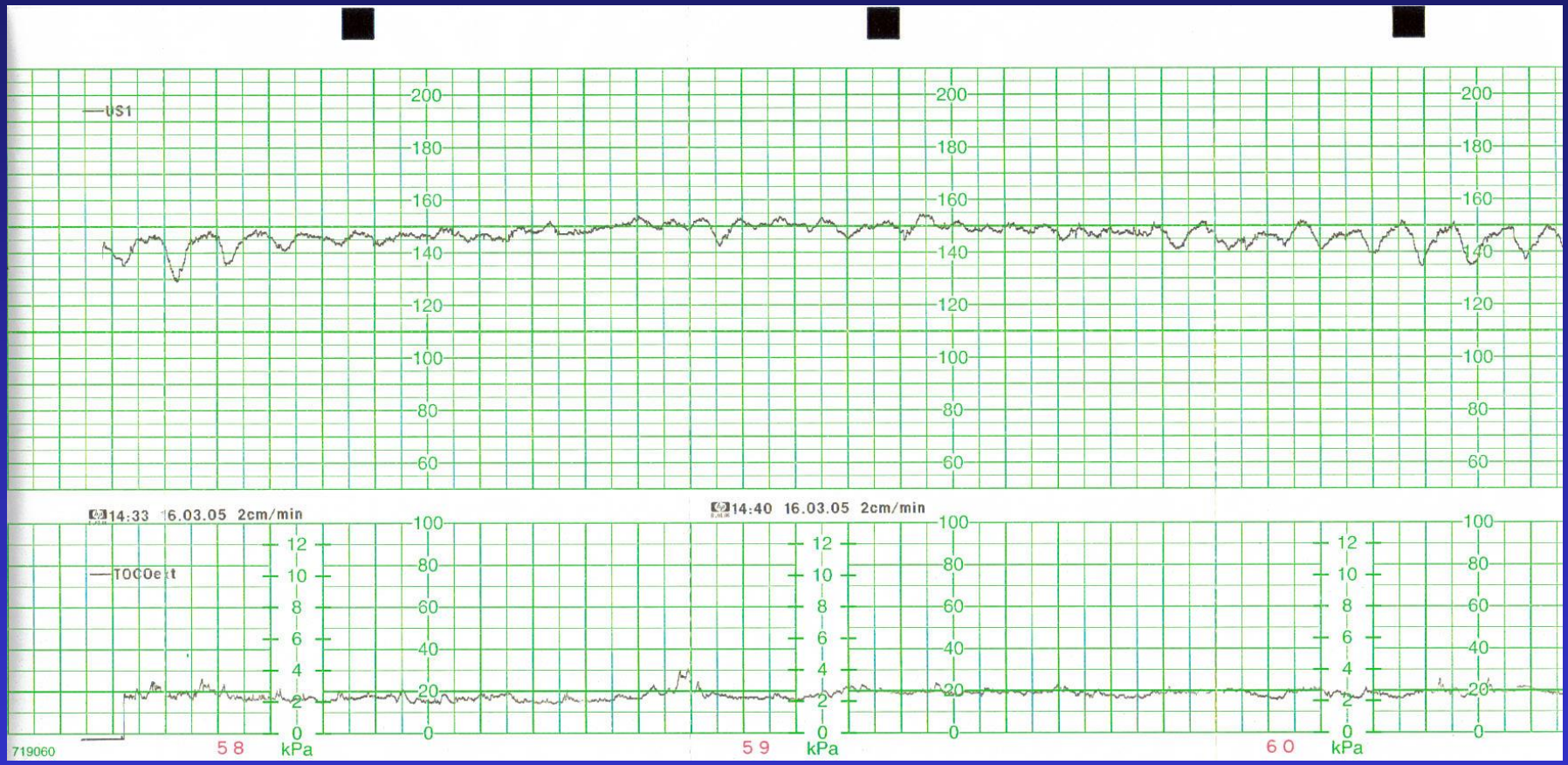
Stillbirth in relation to Perinatal death

Dutch data 2000-2008, >28wks

Antepartum death	72%	stillbirths
Intrapartum death	9%	
Neonatal death	19%	

Vasak et al, U O&G, 2015

CTG-1


US1
200
180
160
140
120
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14:33 16.03.05 2cm/min
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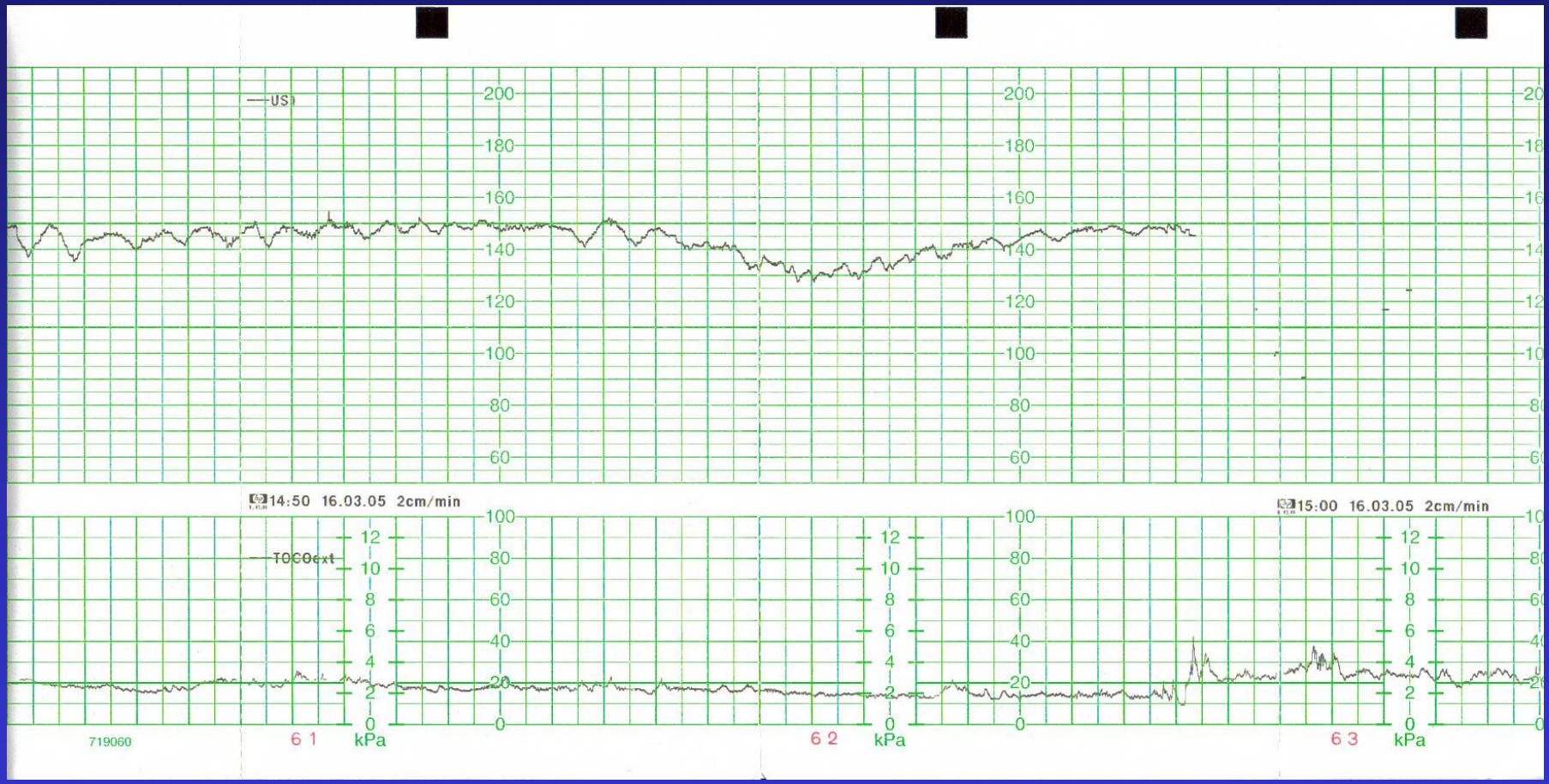
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Start registratie :
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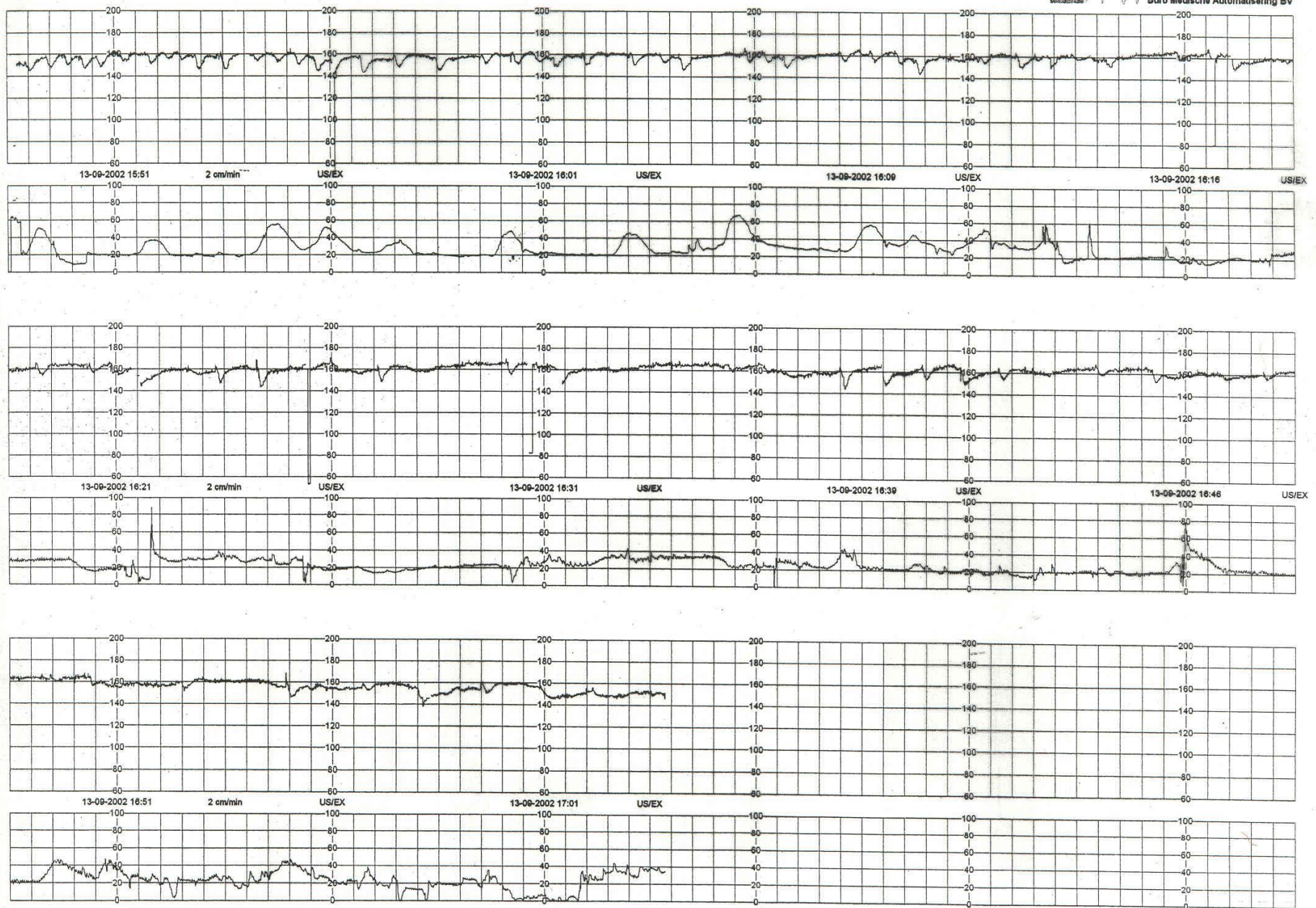

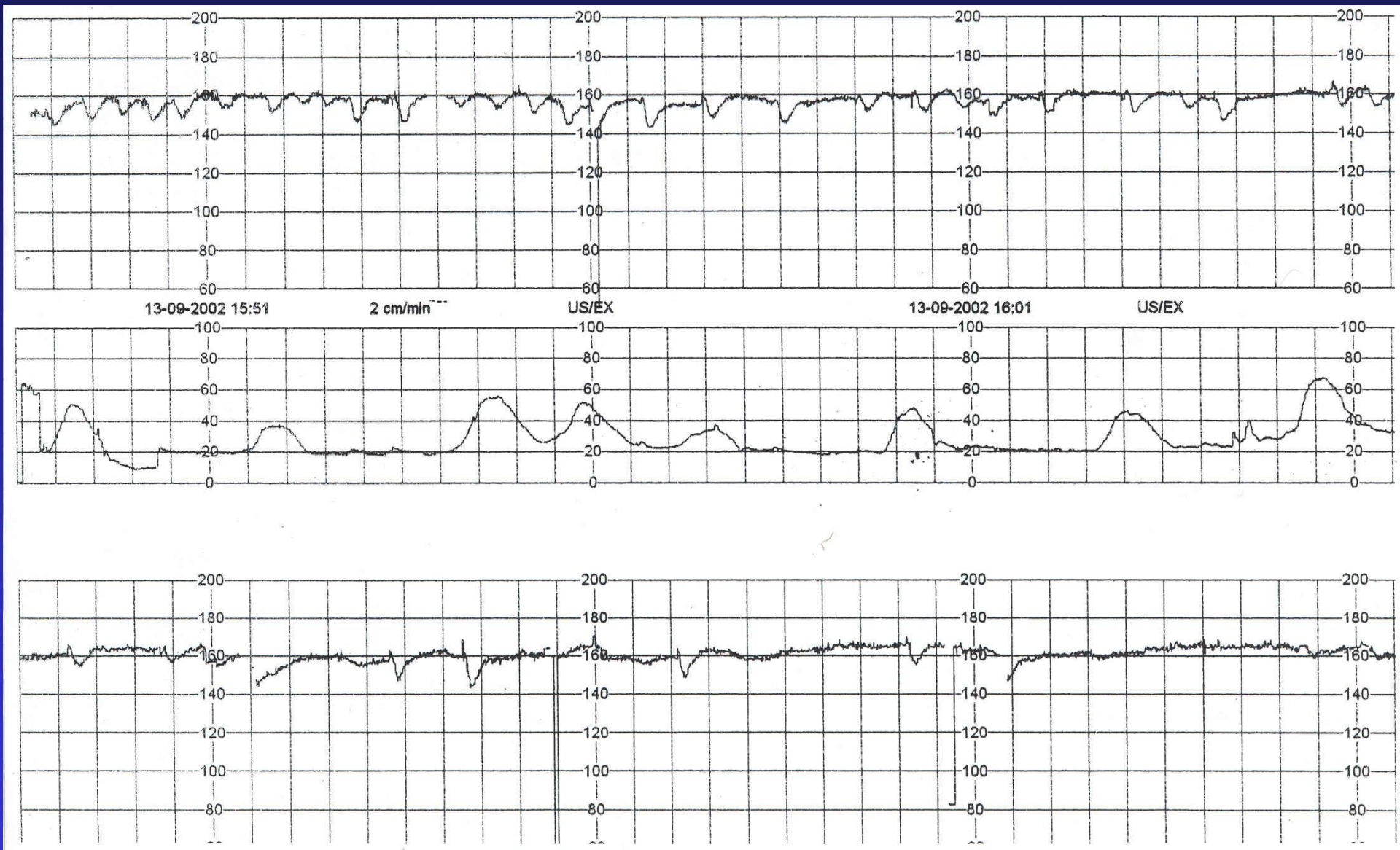
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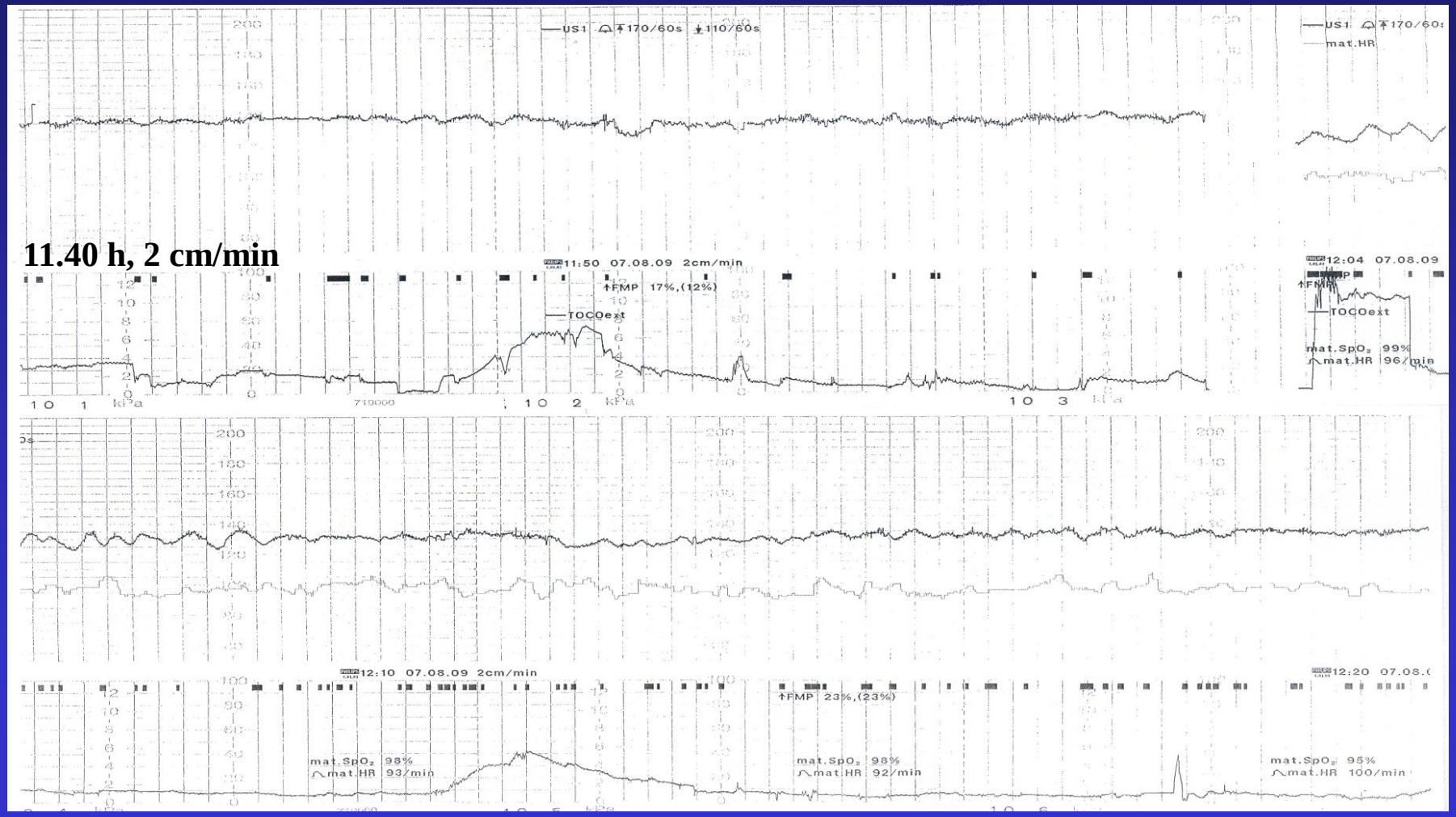
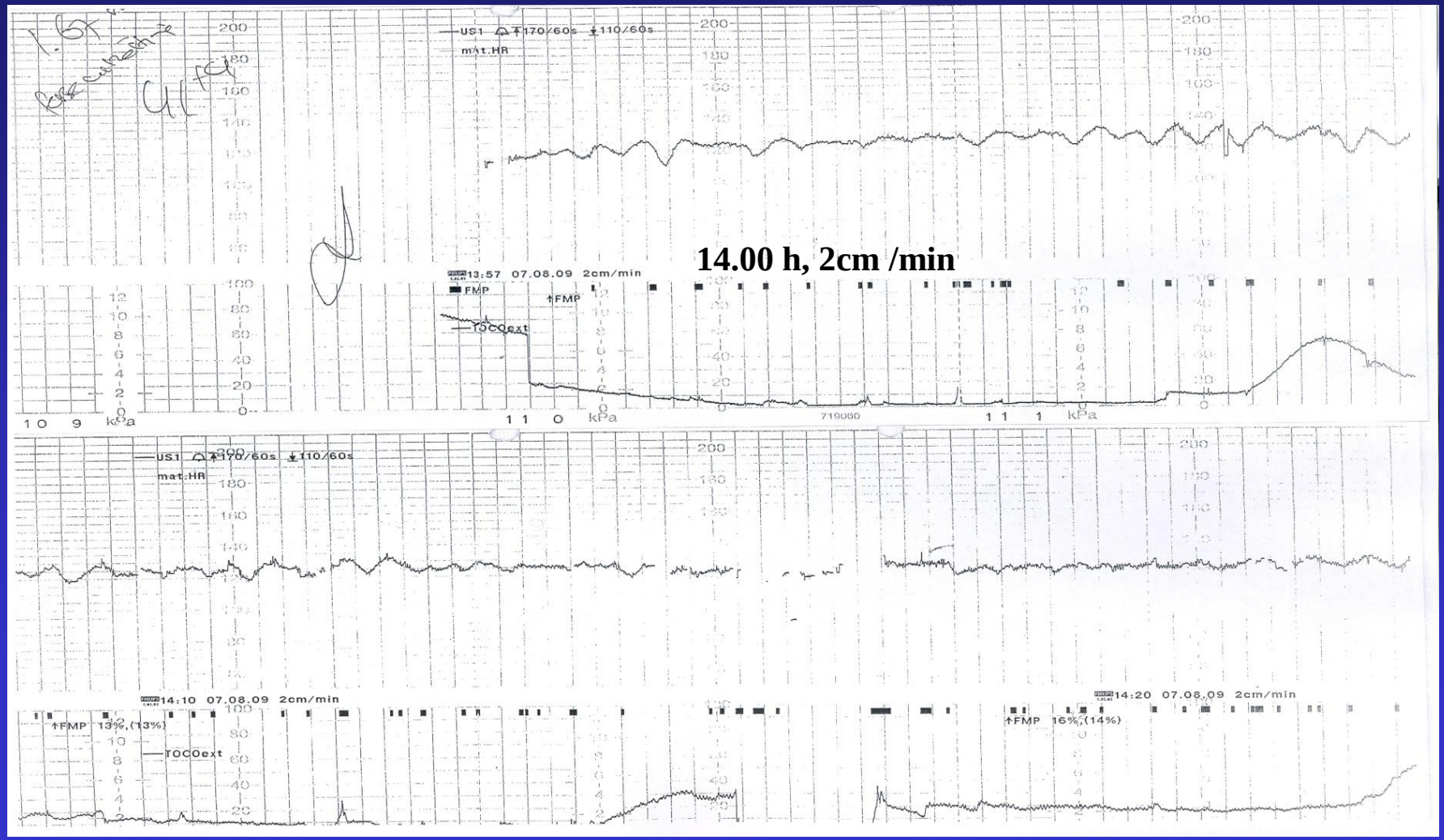
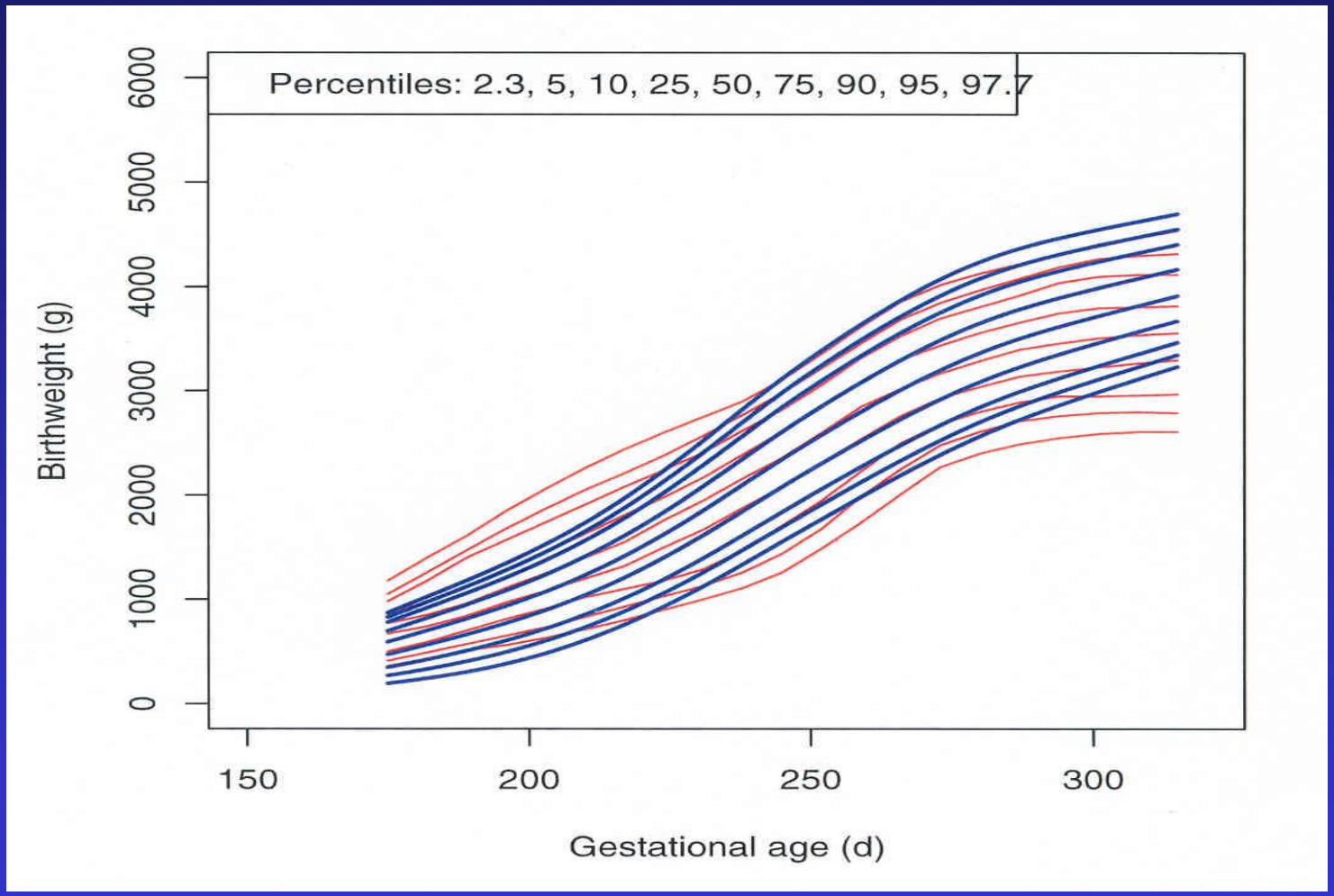
Gr1 P0, 1.66 cm, 95 kg BMI 34.5



Gr1 P0, 1.66 cm, 95 kg BMI 34.5

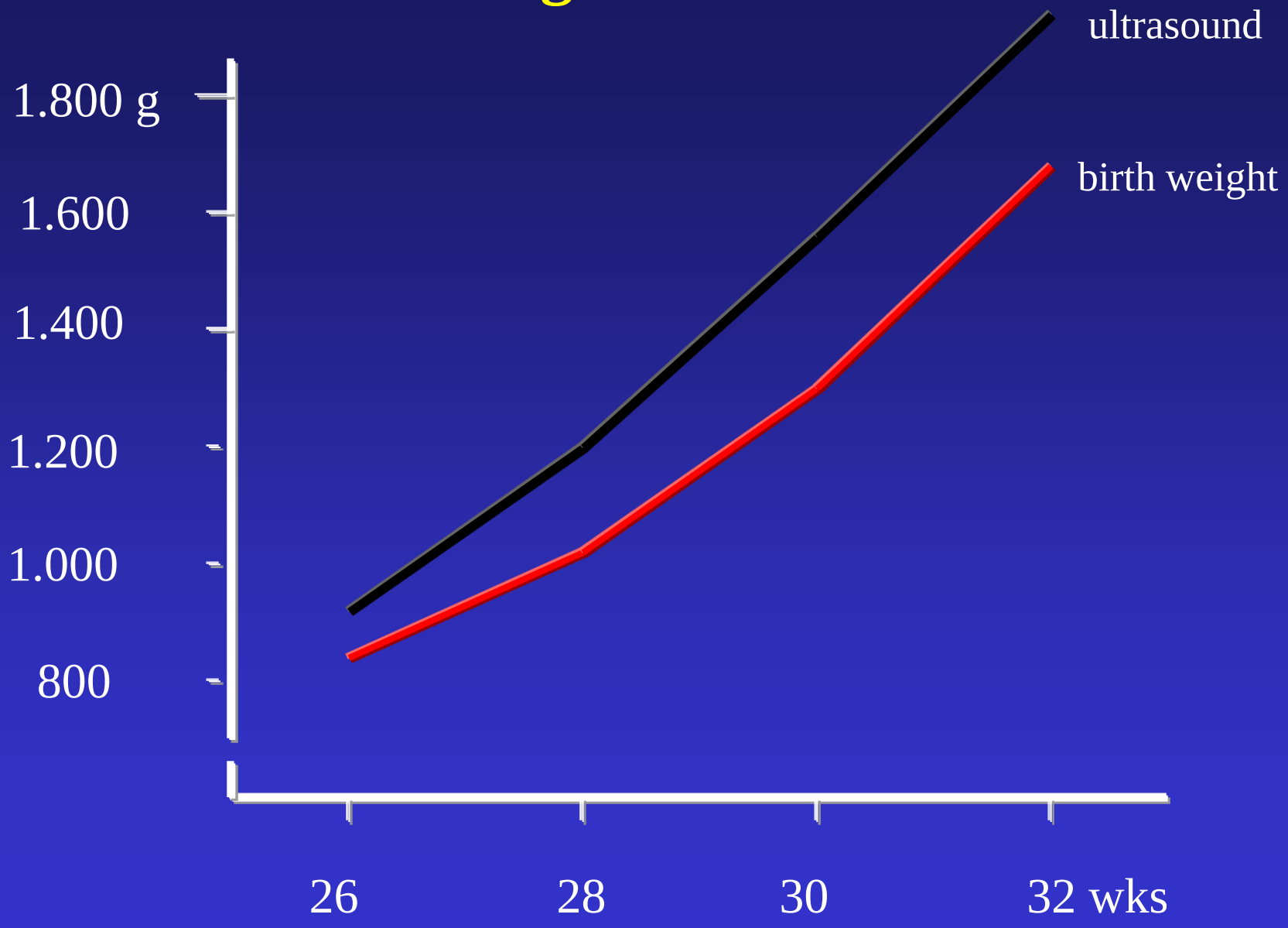


Present and Old Dutch birth weight charts



Visser et al, Early Hum Dev, 2009

50th centile according to ultrasound or birth weight



Visser et al, 2014

Optimal fetal growth

- Fetal growth and weight charts imply that a weight < 10th or > 90th centile identify infants at risk for adverse outcome
- In between the 10th and 90th centile growth/weight is considered normal
- And a weight at the 50th centile is supposed to be optimal.

- **But does that hold true?**

On optimal fetal growth:

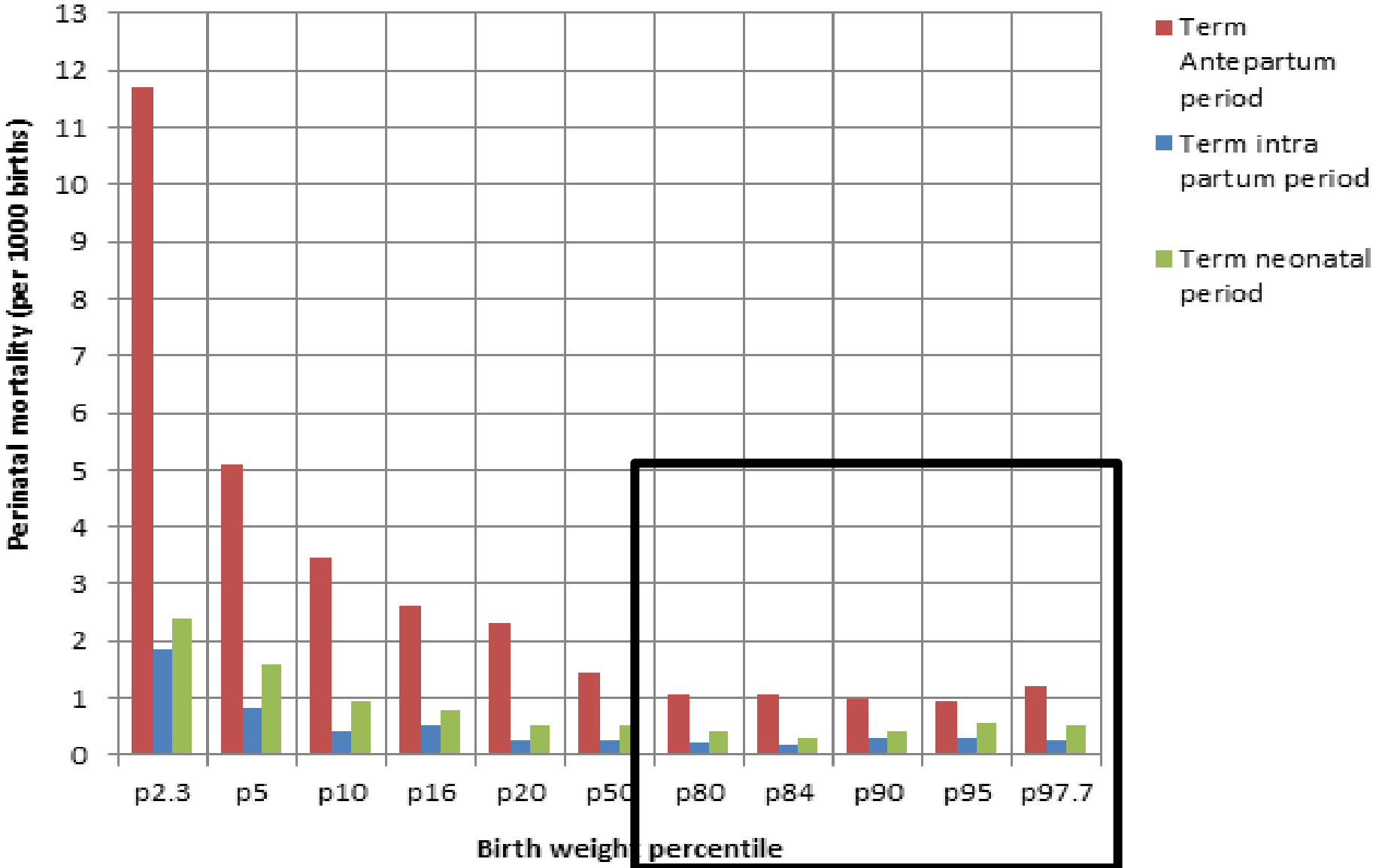
Which birth weight centiles are associated with the lowest perinatal mortality

- Perinatal deaths in the Netherlands (PRN)
- All singletons 2000-2008
- No major malformations
- 28-42 weeks

- N=1.170.127 PNM 5.048 (0.4%)

Vasak et al, Ultrasound O&G, 2015

Perinatal mortality >= 36 wks



1342 Stillbirths > 28 wks gestation; UK

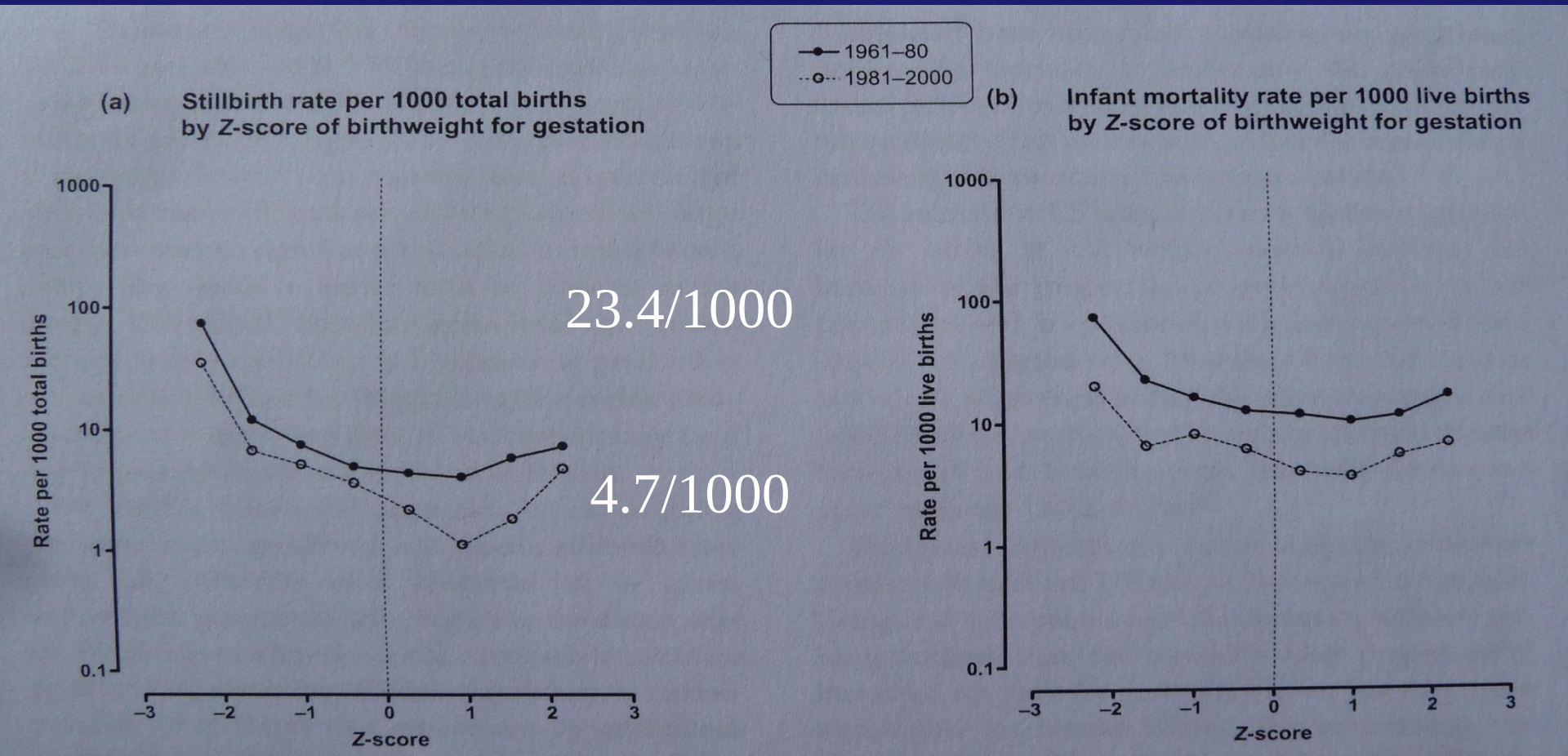


Figure 3. (a) Stillbirth and (b) infant mortality rates (on a log scale) by Z-score of birthweight-for-gestation in singleton births in 1961–80 and 1981–2000, Newcastle upon Tyne.

Glinianaia et al, Paed Perinatal Epidemiol 2010; 24:331-42

Perinatal mortality in relation to birth weight. Nationwide data Norway 1980-1995

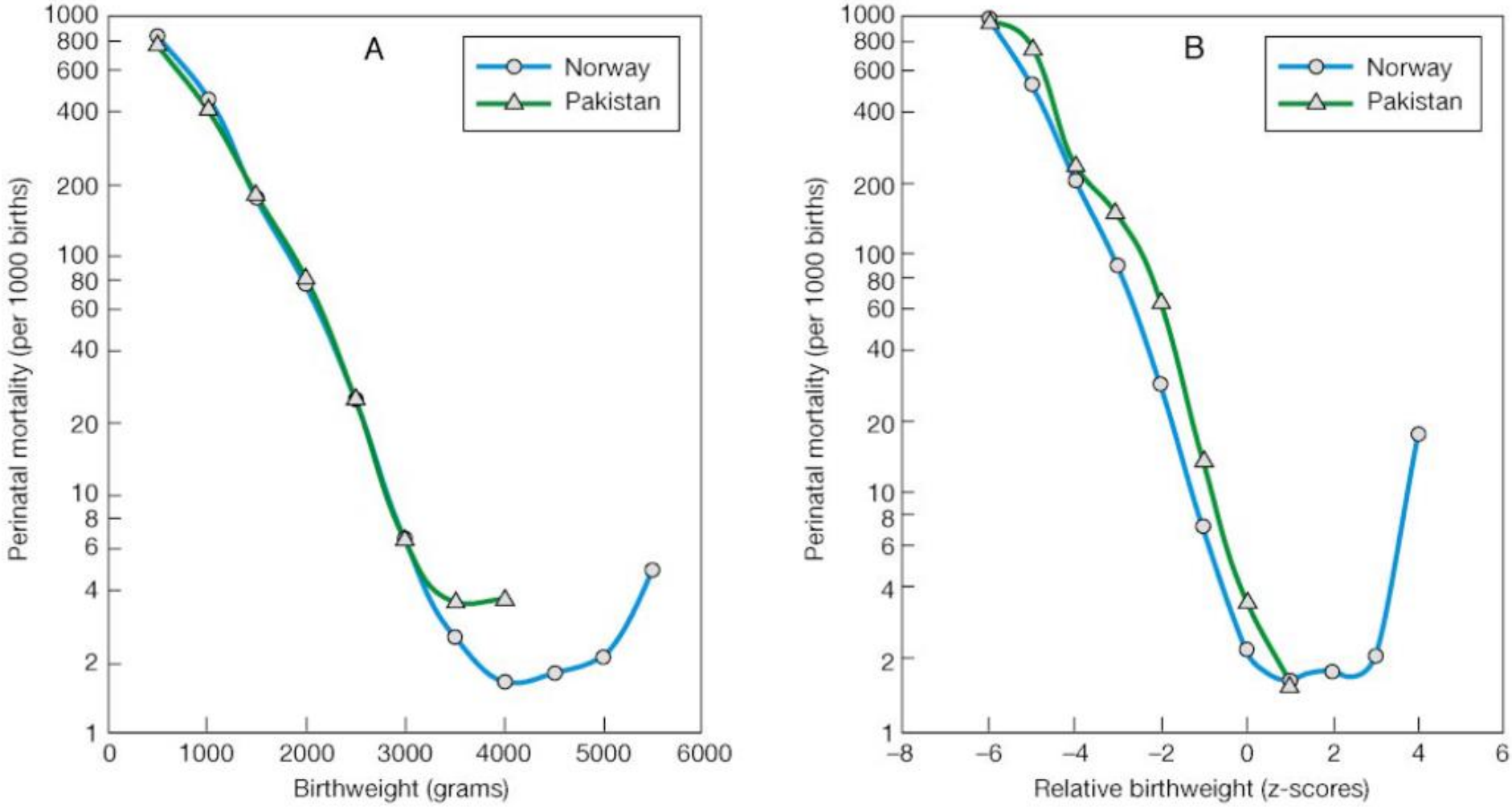


Figure 2 Birthweight-specific mortality before (A) and after (B) adjustment to a relative birthweight scale for Pakistani and Norwegian births, Norway 1980–1995

Vangen et al, Int J Epidemiol 2002

ULTRASOUND
in Obstetrics & Gynecology

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Ultrasound Obstet Gynecol 2015; **45**: 162–167
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Human fetal growth is constrained below optimal for perinatal survival

B. VASAK*, S. V. KOENEN*, M. P. H. KOSTER*, C. W. P. M. HUKKELHOVEN†, A. FRANX*, M. A. HANSON‡ and G. H. A. VISSER*

**Department of Obstetrics, University Medical Center Utrecht, Lundlaan, Utrecht, The Netherlands; †The Netherlands Perinatal Registry, Mercatorlaan, Utrecht, The Netherlands; ‡Institute of Developmental Sciences and NIHR Nutrition Biomedical Research Centre, University of Southampton, Southampton, UK*

KEYWORDS: birth weight; fetal growth; maternal constraint; perinatal mortality; perinatal survival

ABSTRACT

Objective The use of fetal growth charts assumes that the optimal size at birth is at the 50th birth-weight centile, but interaction between maternal constraints on fetal growth and the risks associated with small and large fetal size at birth may indicate that this assumption is not valid for perinatal mortality rates. The objective of

growth. This finding is consistent with adaptations that have evolved in humans in conjunction with a large head and bipedalism, to reduce the risk of obstructed delivery. These data also fit remarkably well with those on long-term adult cardiovascular and metabolic health risks, which are lowest in cases with a birth weight around the 90th centile.

Mother versus father

The battle between the sexes

Question: what do we know on the effect of the father on fetal/placental growth?

On Optimal fetal weight: what about the placenta?

Only with a fetal weight around the 90th centile, all placentas were found to be normal

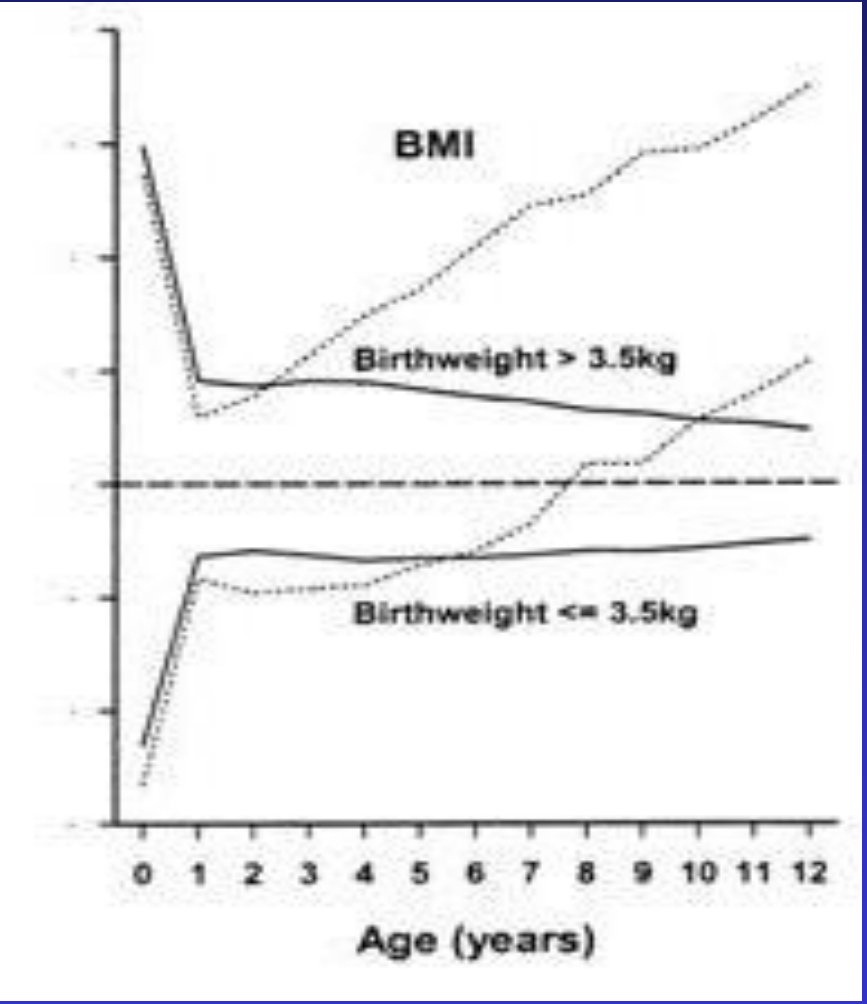
Mecacci et al, Firenze (It); presented in Palermo on May 30, 2014 (Highlights on stillbirth and maternal mortality conference)

So, for short and long term survival

- Birth weight should be around the 90th centile
- And that also holds for weight at age 1-2
- But prevent a rapid weight gain in between the ages of 2 and 7

Birthweight, Infant growth & Type-2 diabetes

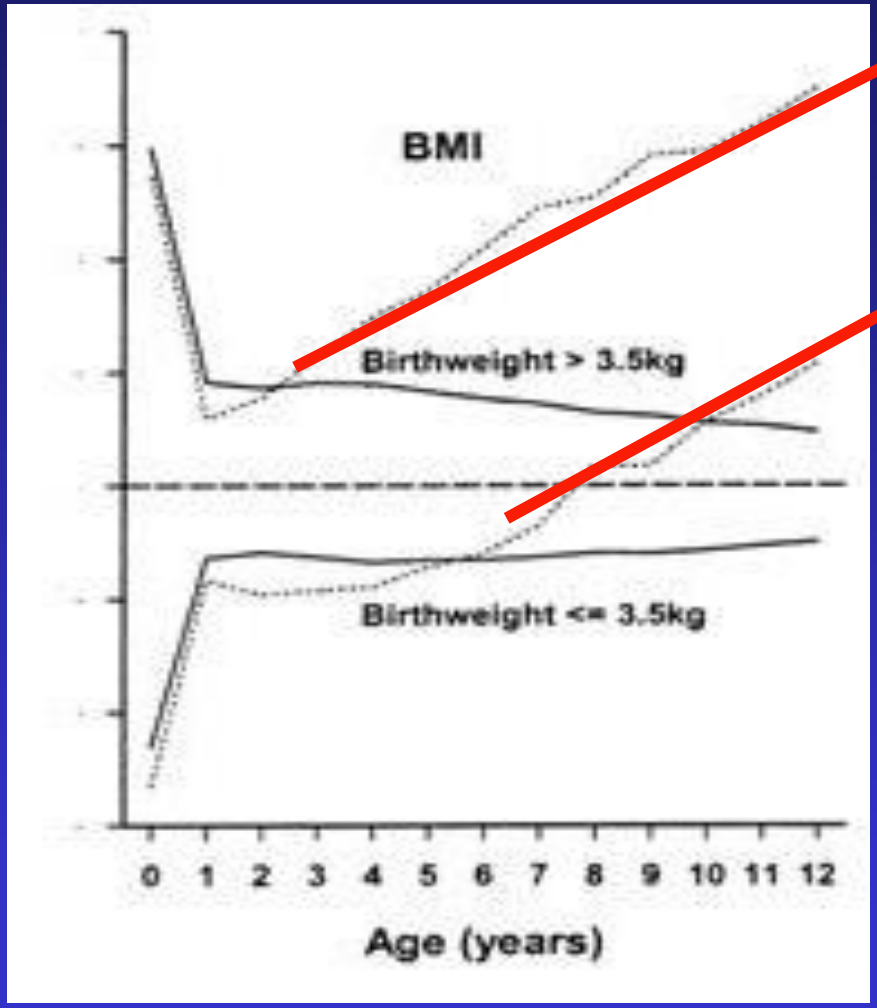
Mean Z-score



(Eriksson et al, Diab Care 2003; 26: 2006-10)

Birthweight, Infant growth & Type-2 diabetes

Mean Z-score



diabetes

(Eriksson et al, Diab Care 2003; 26: 2006-10)

Optimal fetal growth

- Conflict of interest ?
- YES

Birth weight Gerry: 4 kg!

Gerry, 2+ years

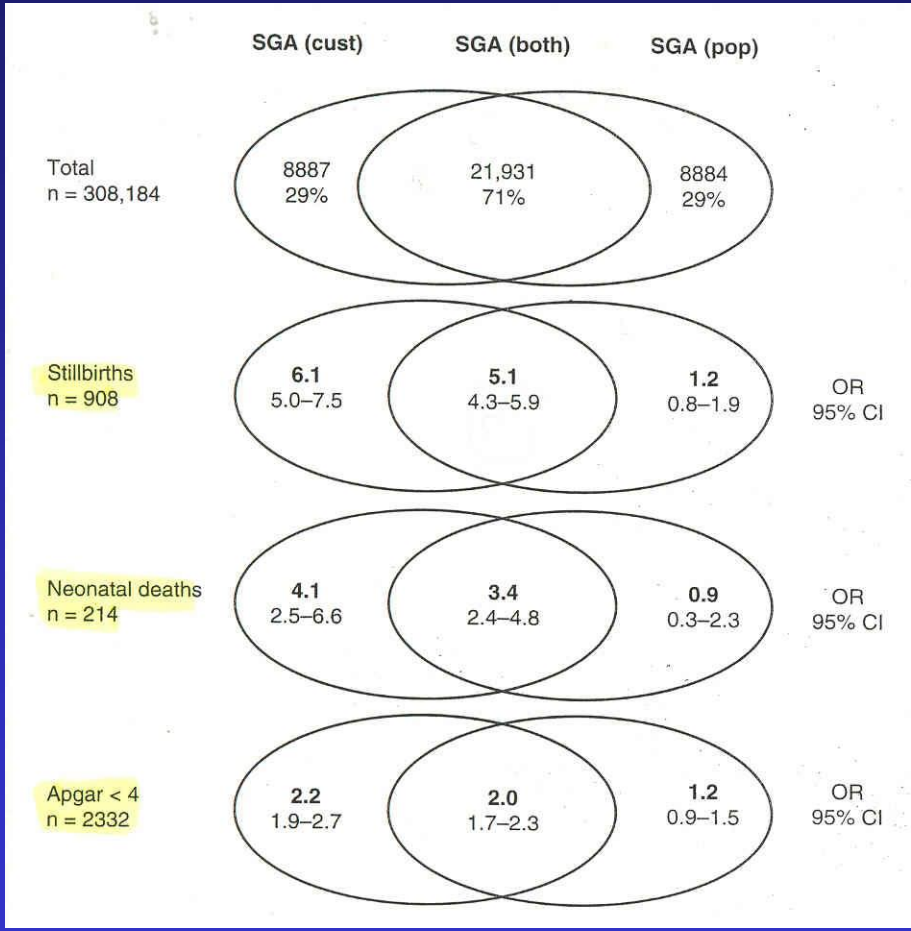

Gerry, 7+ years

Customized assessment of growth

- Charts based on optimal fetal weight at term
- Taking into account:
  - maternal height
  - weight in early pregnancy
  - ethnic origin
  - parity
- Exclusion of factors that effect optimal growth (e.g. smoking)

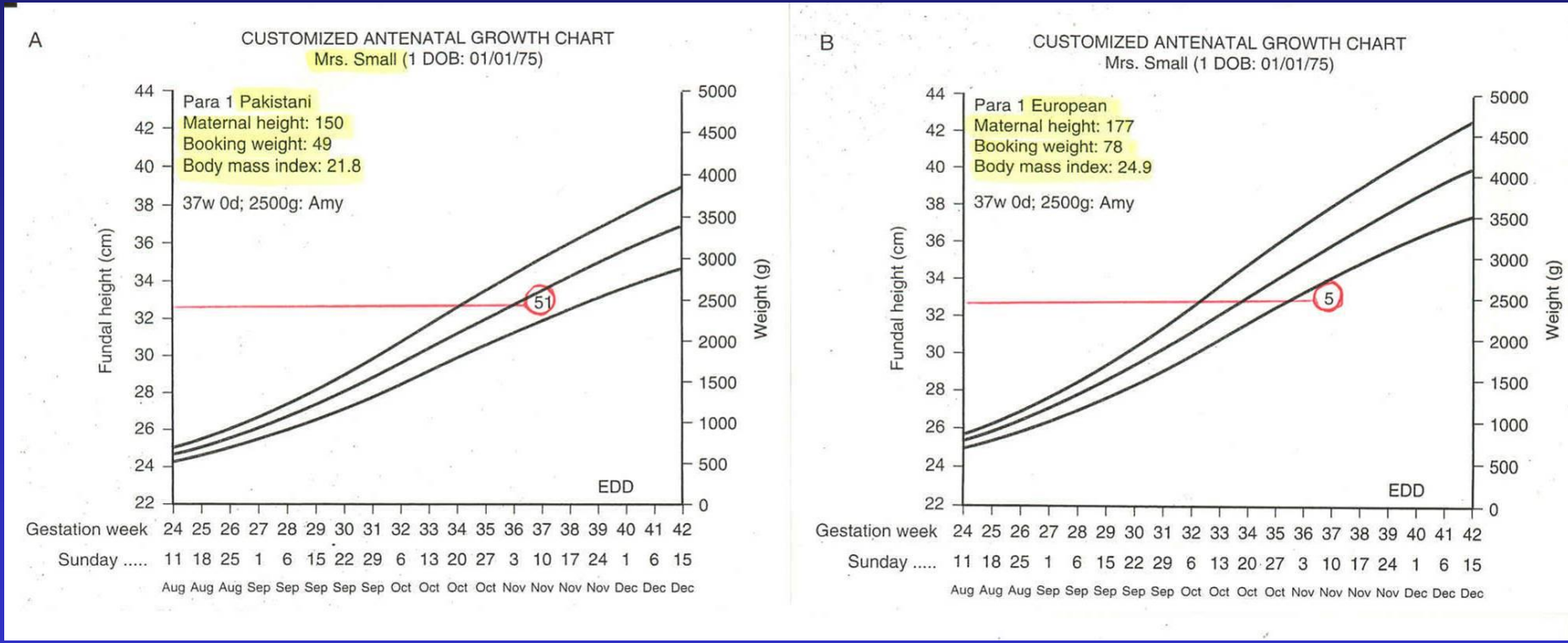
(Gardosi et al, 2005)

SGA customized versus population



(Clausson et al, BJOG 2001; 108: 830-834)

Customized antenatal growth chart



(Gardosi et al, 2005)

Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study

Lancet, 2015

Ulla Sovio, Ian R White, Alison Dacey, Dharmintra Pasupathy, Gordon C S Smith

Findings Between Jan 14, 2008, and July 31, 2012, 4512 women provided written informed consent of whom 3977 (88%) were eligible for analysis. Sensitivity for detection of SGA infants was 20% (95% CI 15–24; 69 of 352 fetuses) for selective ultrasonography and 57% (51–62; 199 of 352 fetuses) for universal ultrasonography (relative sensitivity 2·9, 95% CI 2·4–3·5, p<0·0001). Of the 3977 fetuses, 562 (14·1%) were identified by universal ultrasonography with an estimated fetal weight of less than the 10th percentile and were at an increased risk of neonatal morbidity (relative risk [RR] 1·60, 95% CI 1·22–2·09, p=0·0012). However, estimated fetal weight of less than the 10th percentile was only associated with the risk of neonatal morbidity ($p_{interaction}$=0·005) if the fetal abdominal circumference growth velocity was in the lowest decile (RR 3·9, 95% CI 1·9–8·1, p=0·0001). 172 (4%) of 3977 pregnancies had both an estimated fetal weight of less than the 10th percentile and abdominal circumference growth velocity in the lowest decile, and had a relative risk of delivering an SGA infant with neonatal morbidity of 17·6 (9·2–34·0, p<0·0001).

Interpretation Screening of nulliparous women with universal third trimester fetal biometry roughly tripled detection of SGA infants. Combined analysis of fetal biometry and fetal growth velocity identified a subset of SGA fetuses that were at increased risk of neonatal morbidity.

Neonatal morbidity in SGA infants

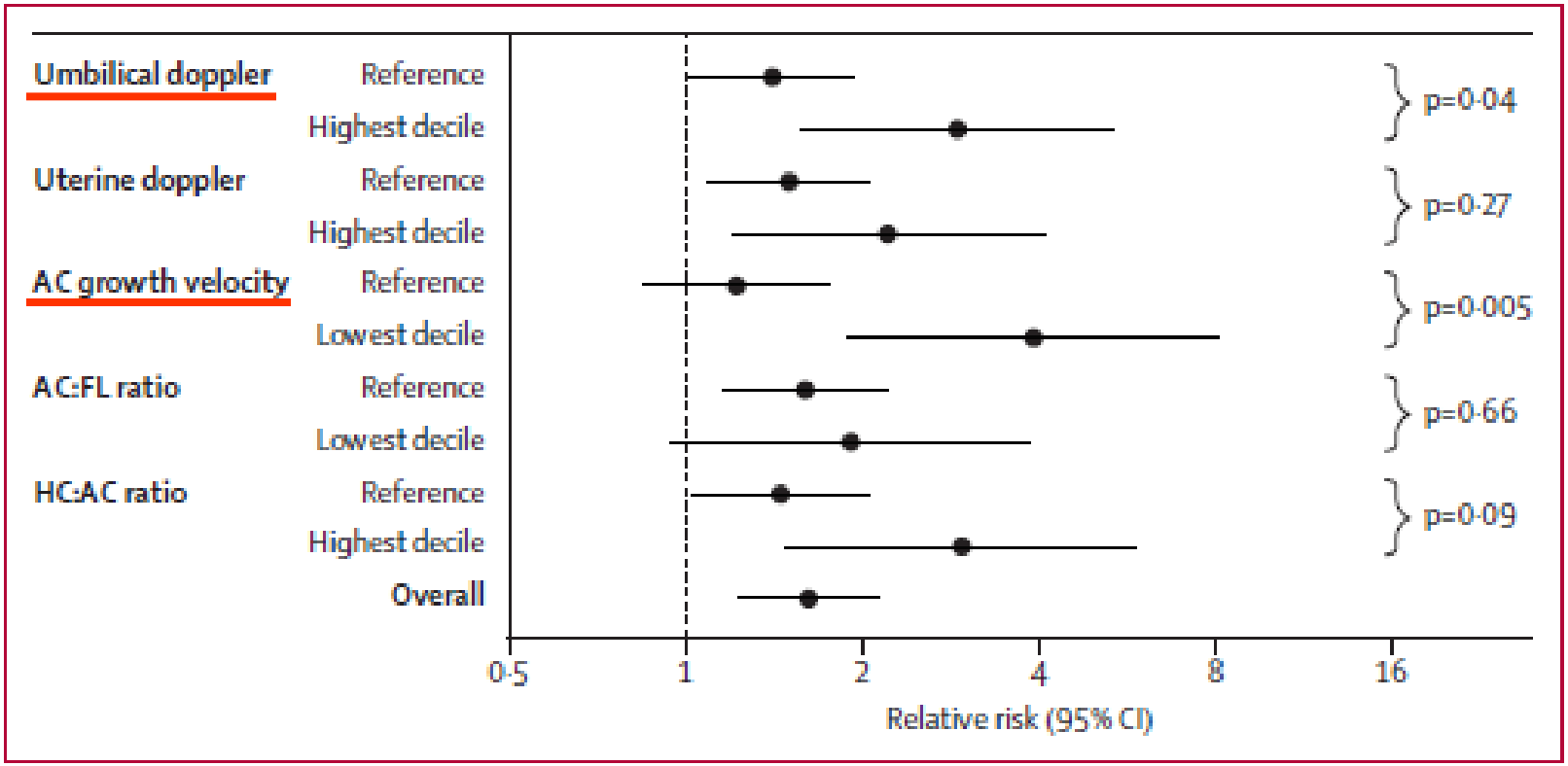
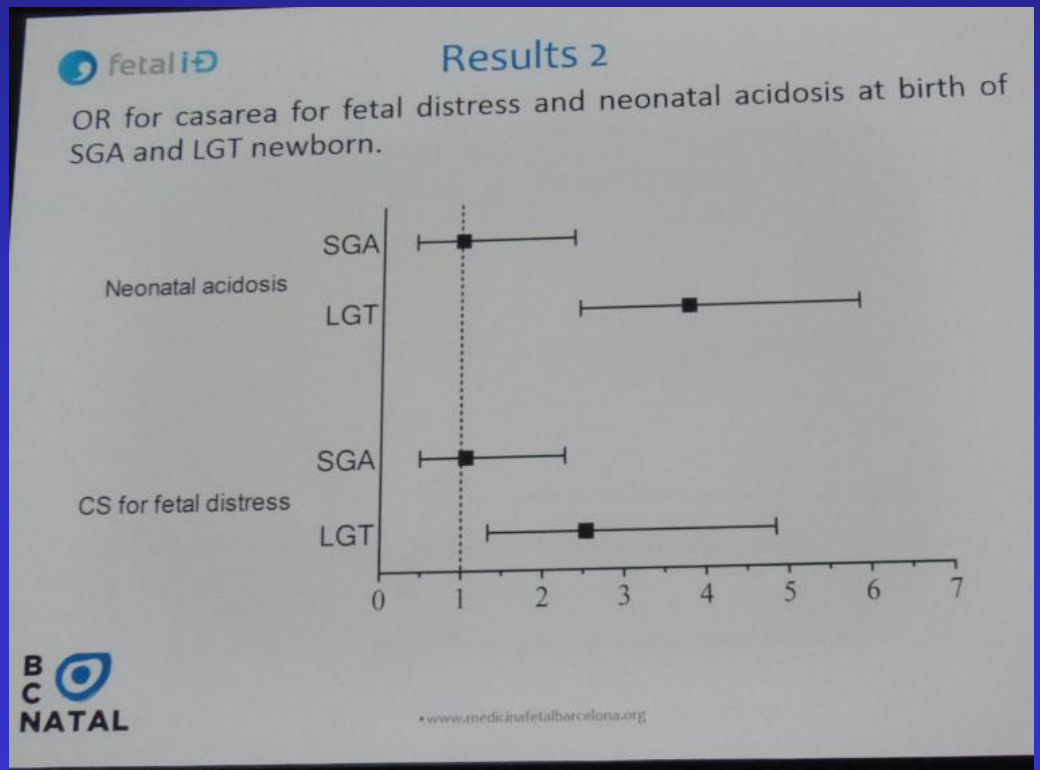


Figure 2: Stratified analyses of the risk of the neonatal composite adverse outcome associated with diagnosis of small-for-gestational-age infants

Sovio et al, Lancet, 2015

Third trimester low growth velocity in AGA fetuses

- Estimated fetal weight > 10th centile at 32-36 wks; n=1004
- Subgroup with subsequent low growth velocity (<10th decile; est. fetal weight at 32-36 wks in comparison to birth weight)



Parra-Saavedra et al, ISUOG, Montreal, Oct 2015

Smoking and stillbirth;

(Gardosi et al, 2013)

Table 2| Smoking and fetal growth restriction (birth weight <10th gestation related optimal weight centile)

Variables	Proportion of total (%)	Stillbirth rate/1000 births
All	100.0	4.2
Smokers:	18.7	5.8
Fetal growth restriction	4.3	13.0
No fetal growth restriction	13.7	3.7
Non-smokers:	81.3	3.8
Fetal growth restriction	8.3	18.3
No fetal growth restriction	68.7	2.1

(Similar data by Moraitis et al, 2014)

Antepartum stillbirth in relation to BW cent

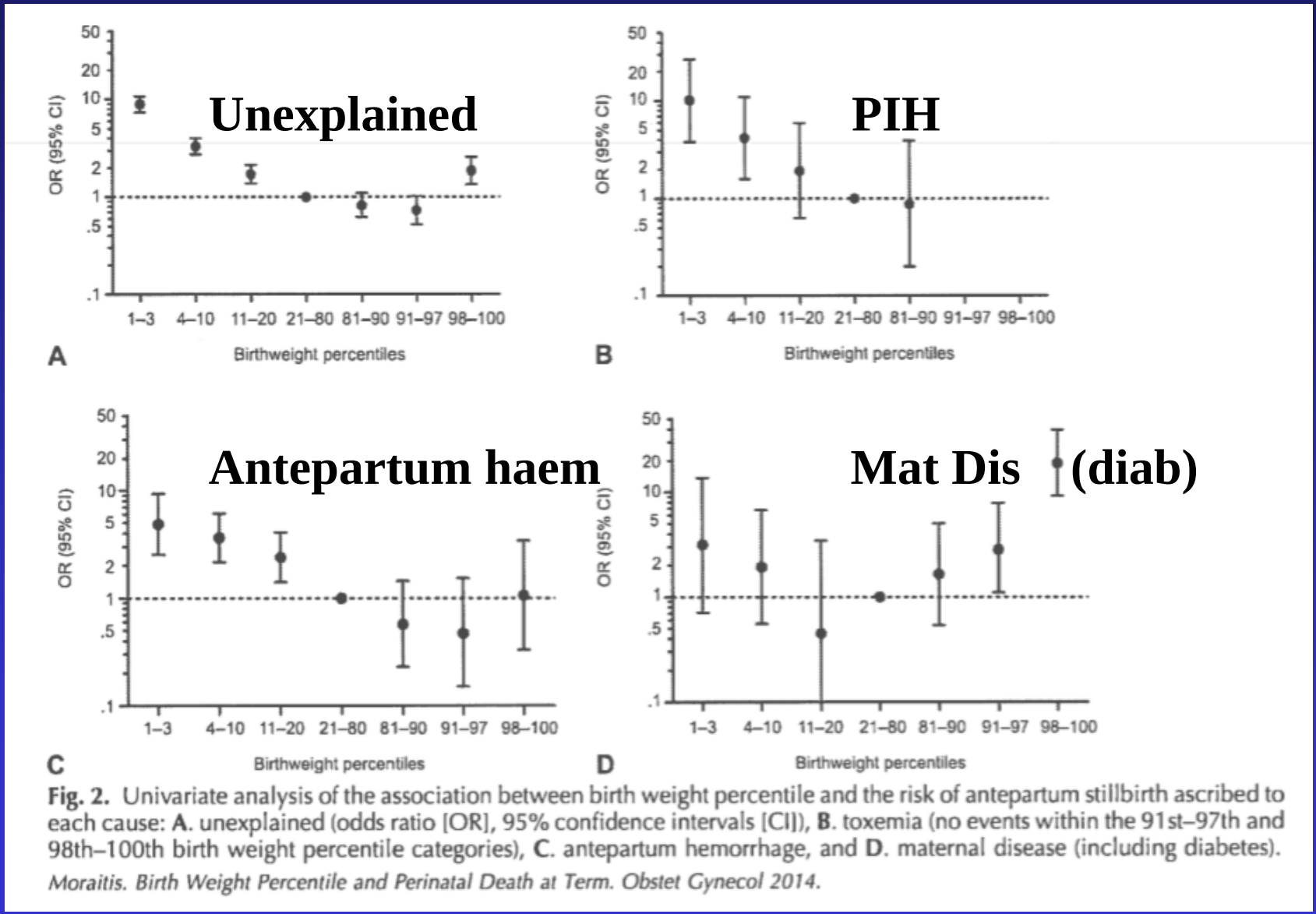


Fig. 2. Univariate analysis of the association between birth weight percentile and the risk of antepartum stillbirth ascribed to each cause: **A**. unexplained (odds ratio [OR], 95% confidence intervals [CI]), **B**. toxemia (no events within the 91st–97th and 98th–100th birth weight percentile categories), **C**. antepartum hemorrhage, and **D**. maternal disease (including diabetes).

Moraitis. Birth Weight Percentile and Perinatal Death at Term. Obstet Gynecol 2014.

Mat height voreggeboorte, lger gewicht
Poor inftant’s outcome if mother dies (zie Vasak & Visser)
Risk assessment is possible at 30-34 wks (Romero PLGF/VEGFR

What is IUGR?

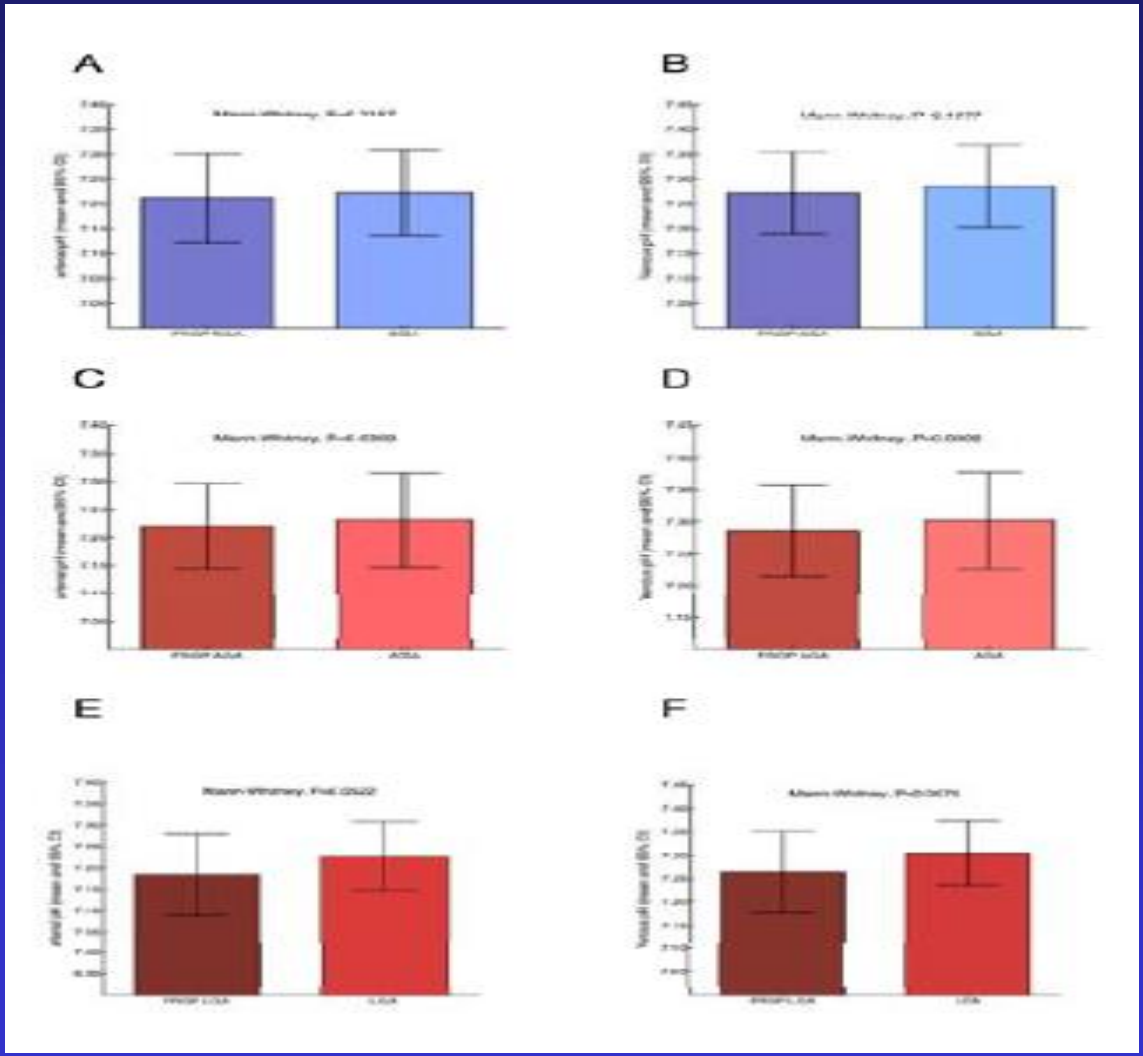
- Fetal growth restriction due to placental insufficiency
- Early IUGR: Abnormal Doppler Umb Art and AC<10th centile (TRUFFLE; PORTO)
- However, that does not cover IUGR with a weight>10th centile
- Late IUGR????

Most late IUGRs are not Small-for-Dates

Late IUGR

- Estimated fetal weight < 2.3rd centile
- AC growth velocity < 10th decile
- Abnormal Cerebro-Placental ratio
- Abnormal Uterine artery PI
- Maternal risk factors

Redistribution and art and venous cord pH



SGA

AGA

LGA

art pH

ven pH

Morales-Rosello et al, 2014

So, for short and long term survival

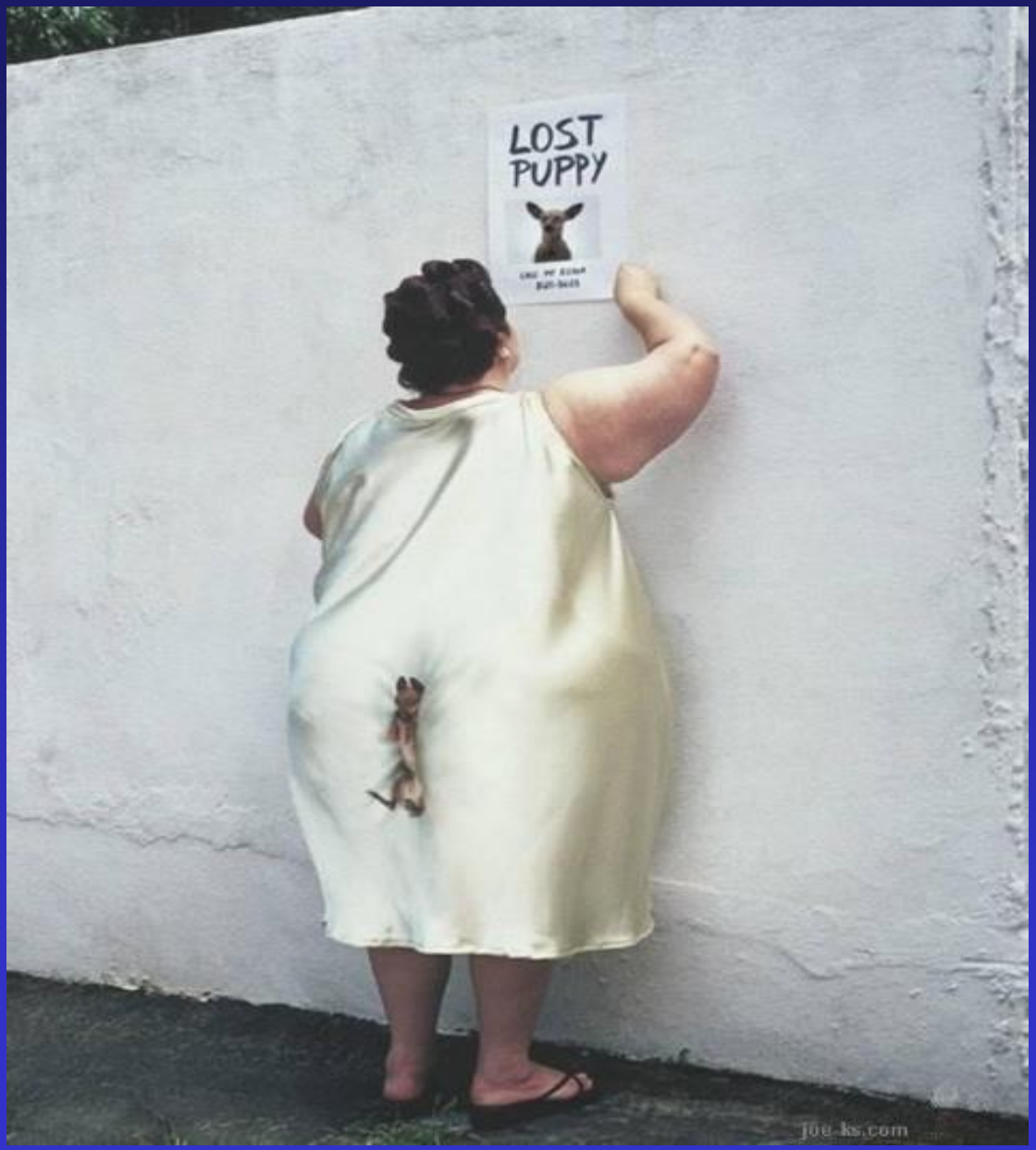
- Your birth weight should be around the 90th centile
- And that also holds for weight at 1-2 y of age
- But prevent a rapid weight gain in between 2 and 7 y of age

And know, that…

- The risk of a term IUFD in a nulliparous 36 years old woman is greater than the risk of her having a child with a chromosomal anomaly

Fretts and Duro, 2008

Individualize, start thinking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What is IUGR?

- Fetal growth restriction due to placental insufficiency

- Early IUGR: Abnormal Umb ArtDoppler PI and AC<10th centile (TRUFFLE; PORTO)
- However, that does not cover IUGR with a weight>10th centile

- Late IUGR????

Identification of the fetus a risk

- helps to prevent perinatal mortality
- At least in SGA fetuses

DIGITAT study

2 y follow up, 50% of the population
Ages and Stage Questionnaire (ASQ and Child Behaviour Checklist (CBCL)

No difference

Van Wijk et al, AJOG 2012, May, 206(5) 406,e1-7

DIGITAT study

- Once SGA has been identified, mortality is low in centers with adequate fetal surveillance
- Lowest morbidity occurred in spontaneous and induced labours at 38 weeks

Van Wijk et al, AJOG 2012, May, 206(5) 406,e1-7

Term IUGR/SFD

- **Assessment techniques:**

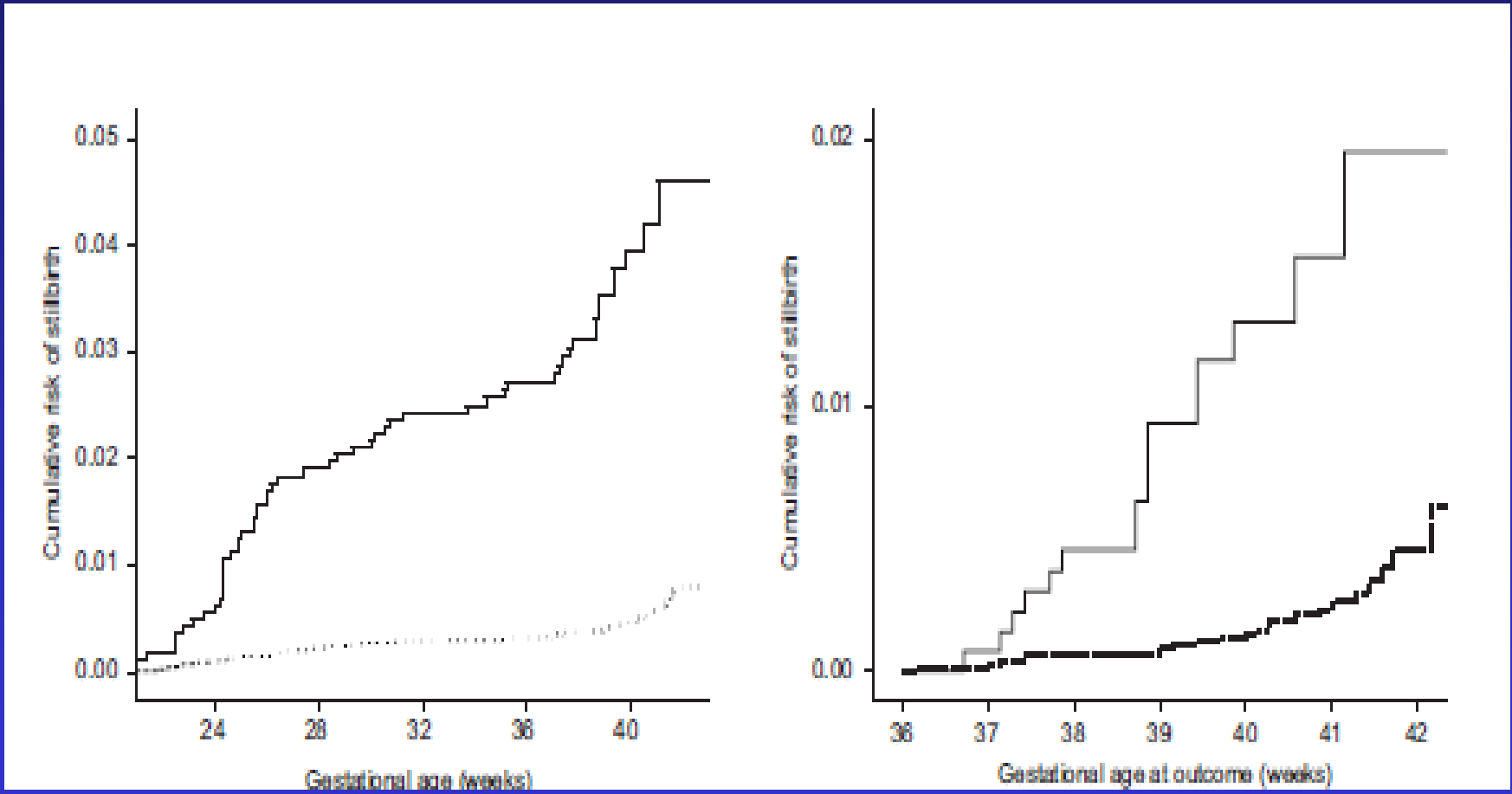
- Fundal height
- Ultrasound fetal size
- Amniotic fluid
- Cardiotocography
- Fetal movements !!

Identification of the late IUGR fetus

- 1- First trimester risk screening
- 2- 20 and 30 wks uterine artery (+ placenta proteins?)
- 3- 30+ wks in case 1 and/or 2 are abnormal: longitudinal growth assessment
- 4- 30+ wks, if growth <25th centile or falling:
  - .. MCA/Umb artery ratio
  - .. FHR acceleration capacity

Delivery 38 wks, or before (CTG changes)

Cumulative stillbirth risk according to ut artery PI at 19-23 wks



Singh et al, O & G, 2012

IUGR contingency screening

- **Combined screening at 11-13 wks**
- (history, MAP, UtPI, PLGF,PAPP-A)
- High Risk (20%) Low Risk (80%)
- Aspirin
- **Combined screening at 22 wks**
- (UtPI, Umb aPI, MAP, serum PLGF/sFLT-1)
- High Risk (…%) Moderate Risk (…%) Low Risk (…%)
- See every 2 wks
- **Combined screening at 32 weeks**
- (UtPI, MAP, serum PLGF ,ultras customised fetal weight)
- High Risk (…%) Low Risk (…%)
- See every 1 wk: fetal growth, MCA/Umb artPI nothing else

Cerebral palsy in preterm and term SFD* infants; population based study; 334 infants with CP

	OR
• Early preterm <34 wks	0.8 (0.4-1.4)
• Late preterm 34-37 wks	1.1 (0.4-3.4)
• Term >37 wks	5.2 (2.7-10.1)

*customised, < 10th centile preterm, < 5th centile term; Jacobsson et al BJOG,2008

Perinatal mortality in relation to birth weight. Nationwide data Norway 1980-1995

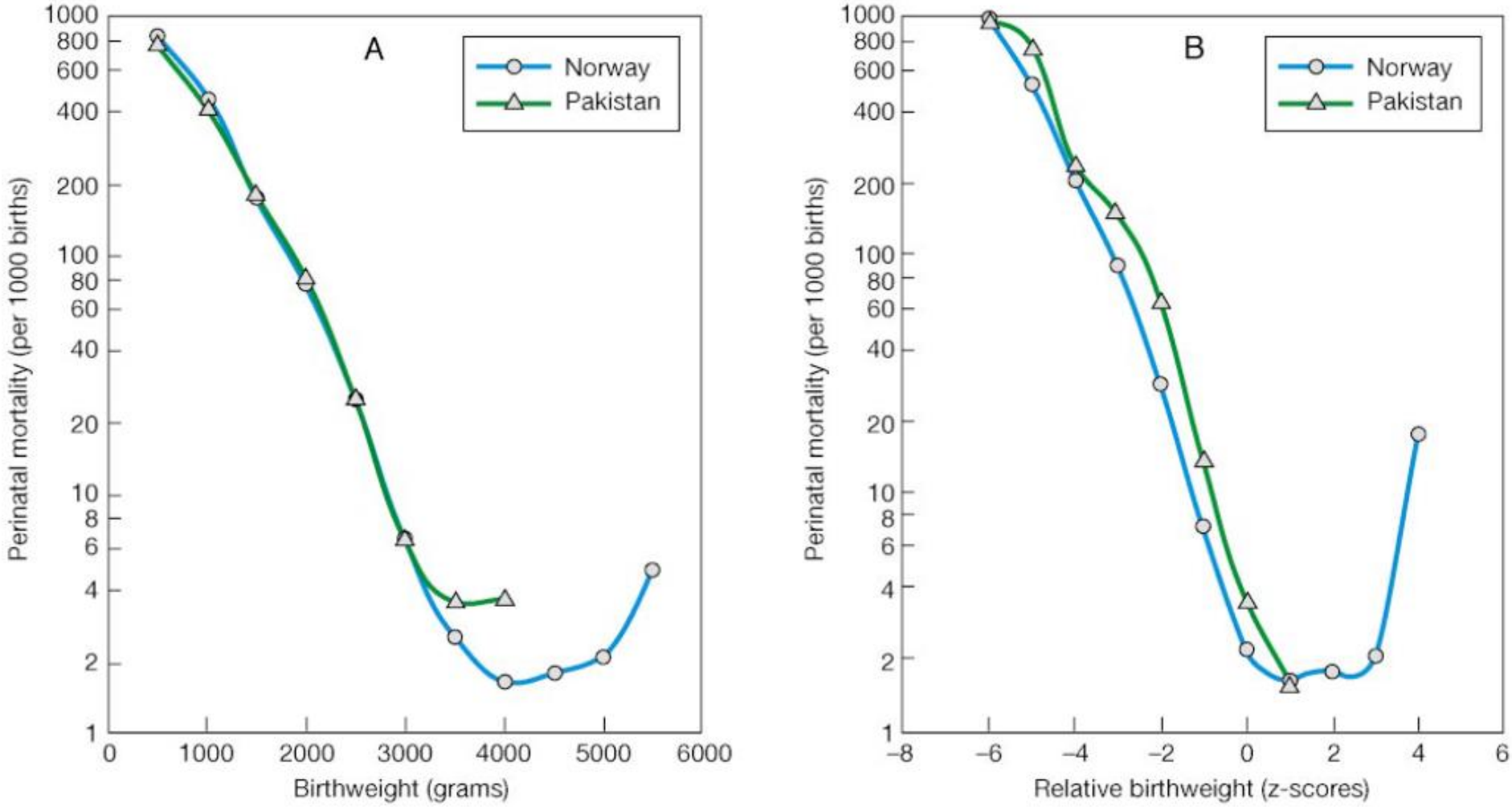


Figure 2 Birthweight-specific mortality before (A) and after (B) adjustment to a relative birthweight scale for Pakistani and Norwegian births, Norway 1980–1995

Vangen et al, Int J Epidemiol 2002

Perinatal mortality in relation to birth weight (centiles)

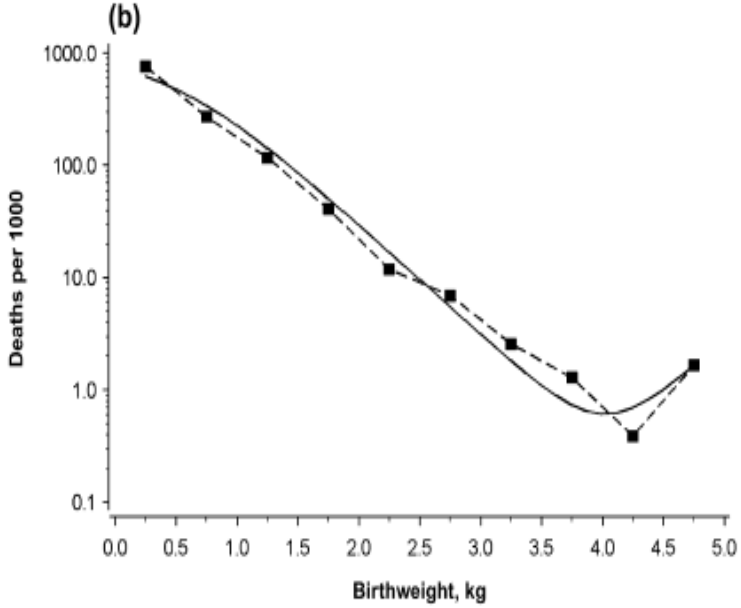


Figure 3. Observed mortality by birthweight in increments of 500 g (dotted lines) and estimated mortality risk using a combination of two linear logistic risk functions (solid lines). (a) Murmansk County; (b) Northern Norway.

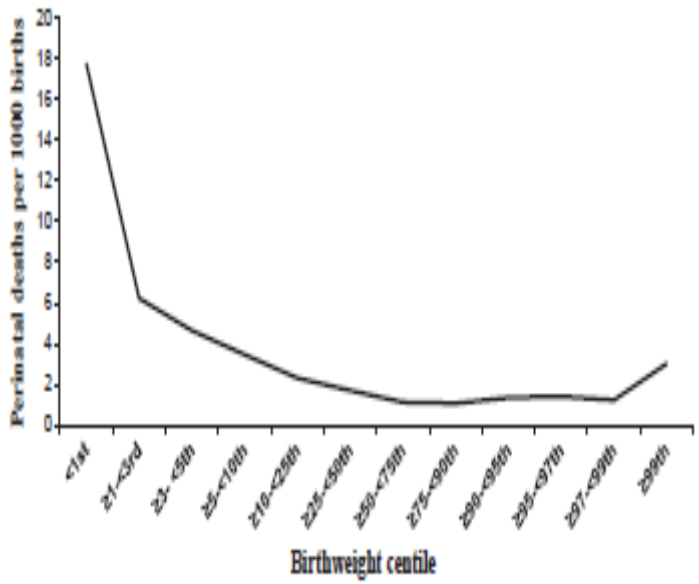


Figure 1 Perinatal death by birthweight centile per 1000 births for term singletons, Victoria 1999–2008.

Anda et al, Paed &Perin Epidemiol 2011;

Francis et al, Austr NZ J Obstet Gynaecol 2014

	Identification	Prevention mortal/morb
Early IUGR	easy	difficult
Late IUGR/SGA	difficult	easy

Late onset IUGR; uterine artery

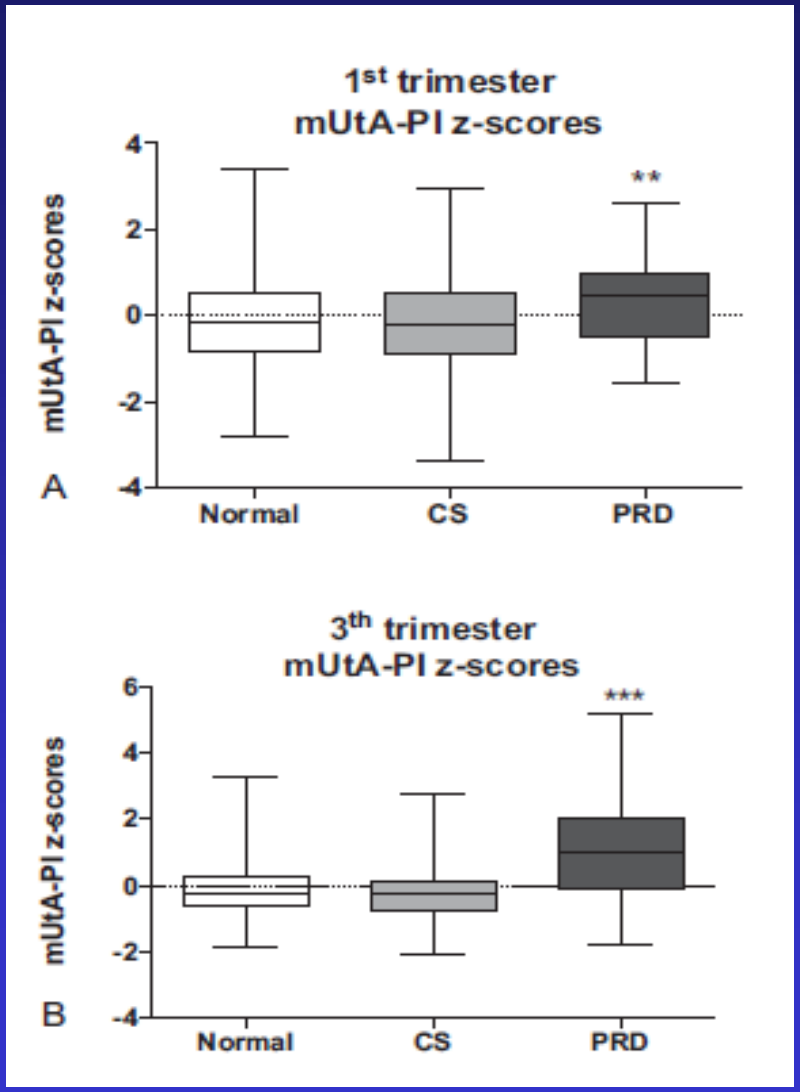
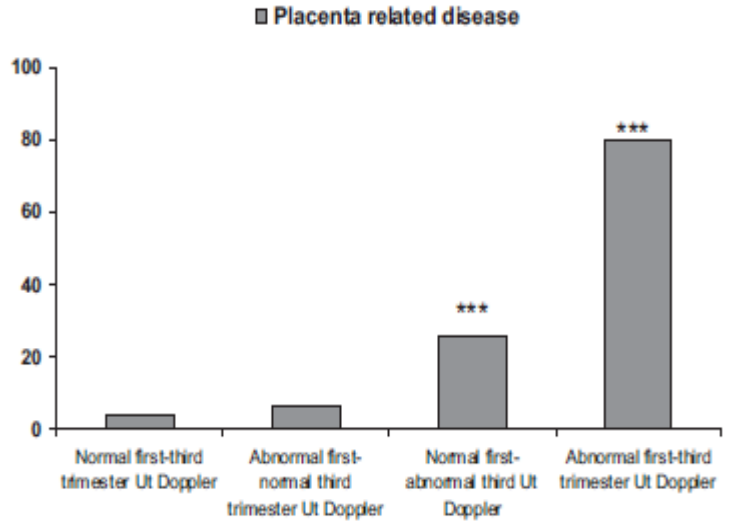


Table 4 Concordance between first- and third-trimester abnormal mUtA-PI z-scores

mUtA-PI z-scores	Third trimester	
	normal (<2 SD)	abnormal (≥2 SD)
First trimester, normal (<2 SD)	878	31
First trimester, abnormal (≥ 2SD)	31	5

mUtA-PI, mean uterine artery pulsatility index; SD, standard deviation.



Llurba et al, Am J Perinatology, 2013

Longitudinal changes in uterine, umbilical and cerebral Dopplers in late onset SGA

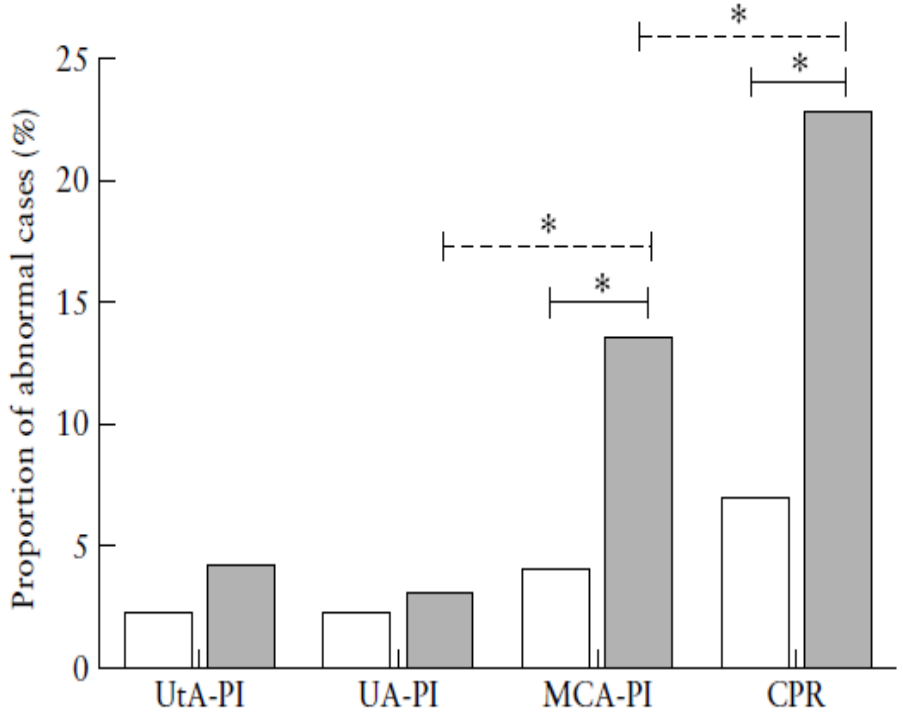
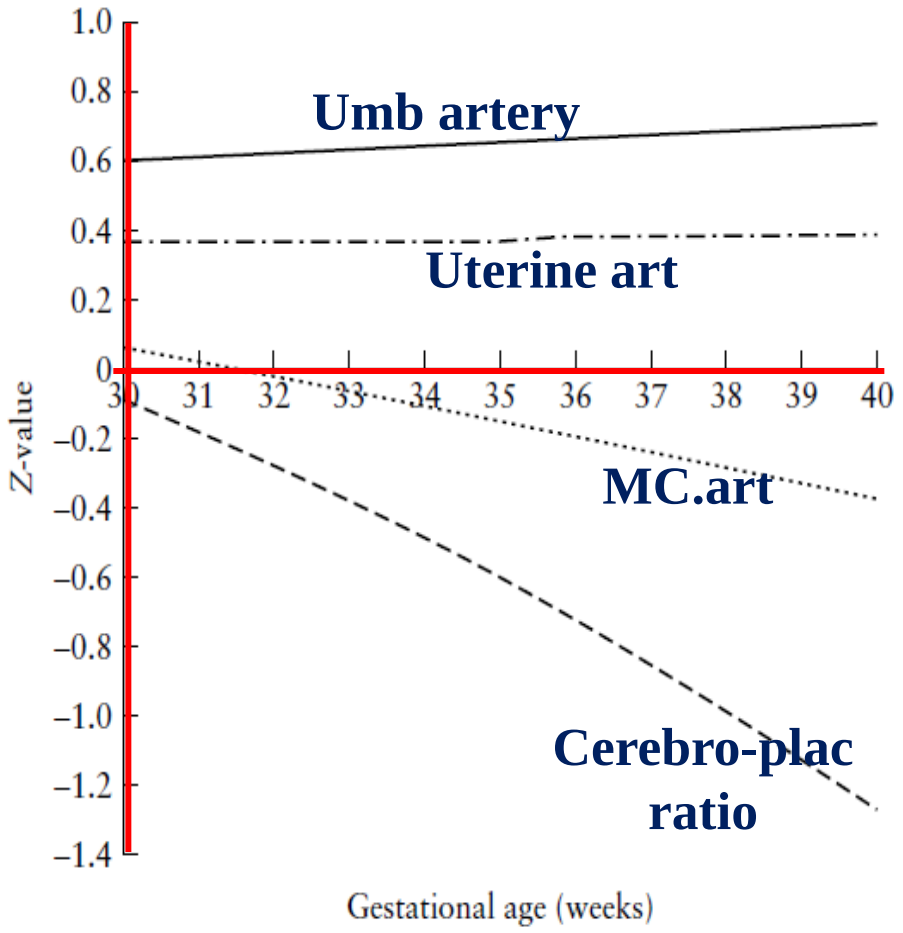
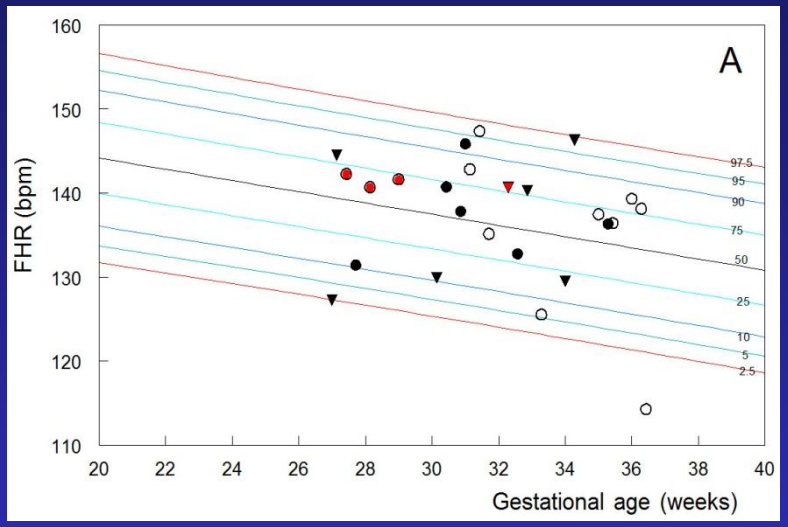


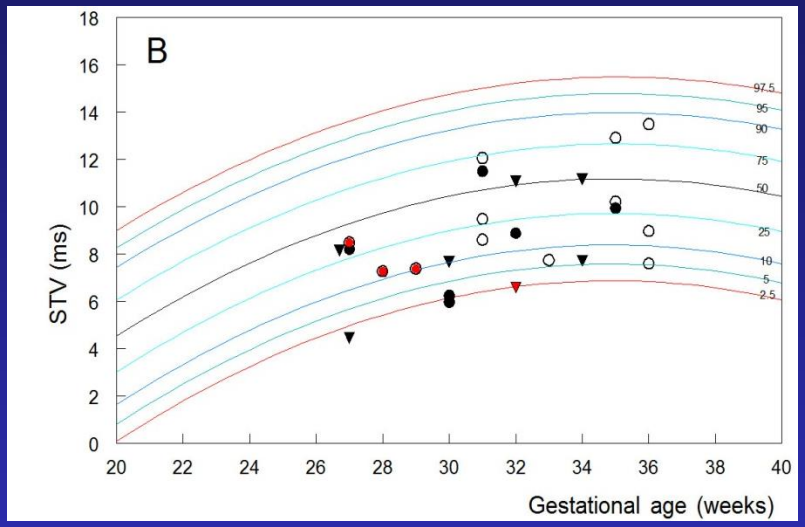
Figure 1 Proportion of abnormal Doppler findings at 37 weeks' gestation (□) and last examination before delivery (■) (*McNemar $P < 0.05$). CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

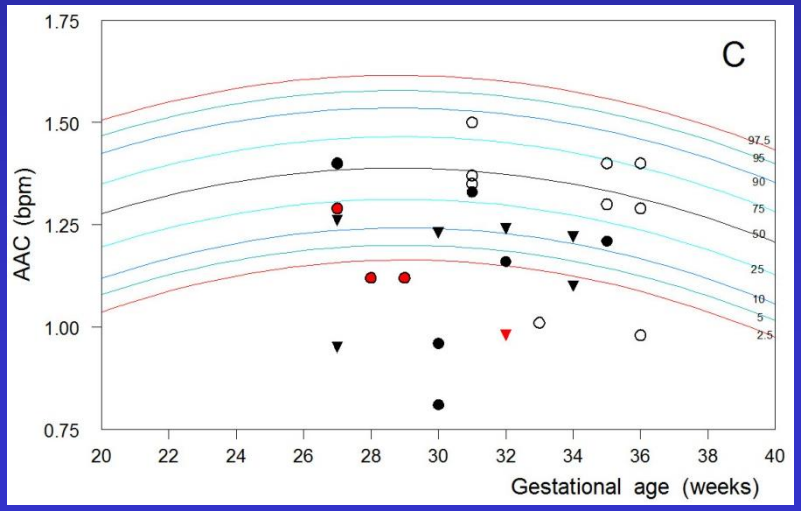


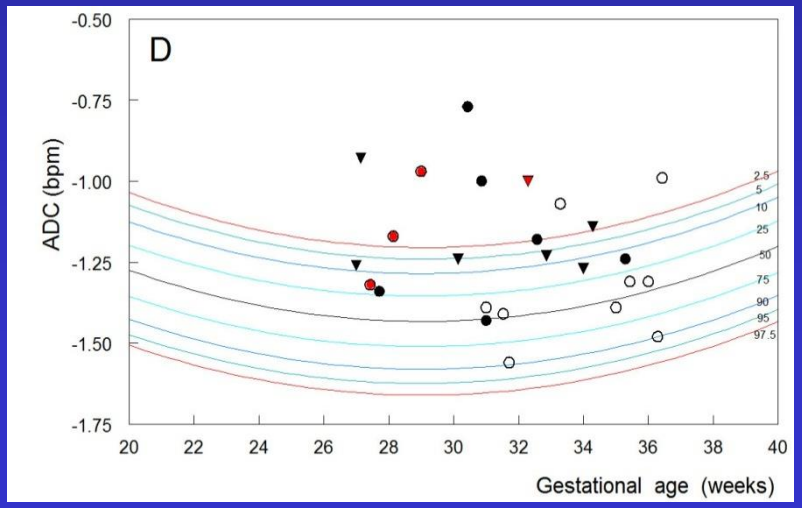
Oros et al, UOG 2010

FHR, STV , ACC and ADC in SFD/IUGR fetuses



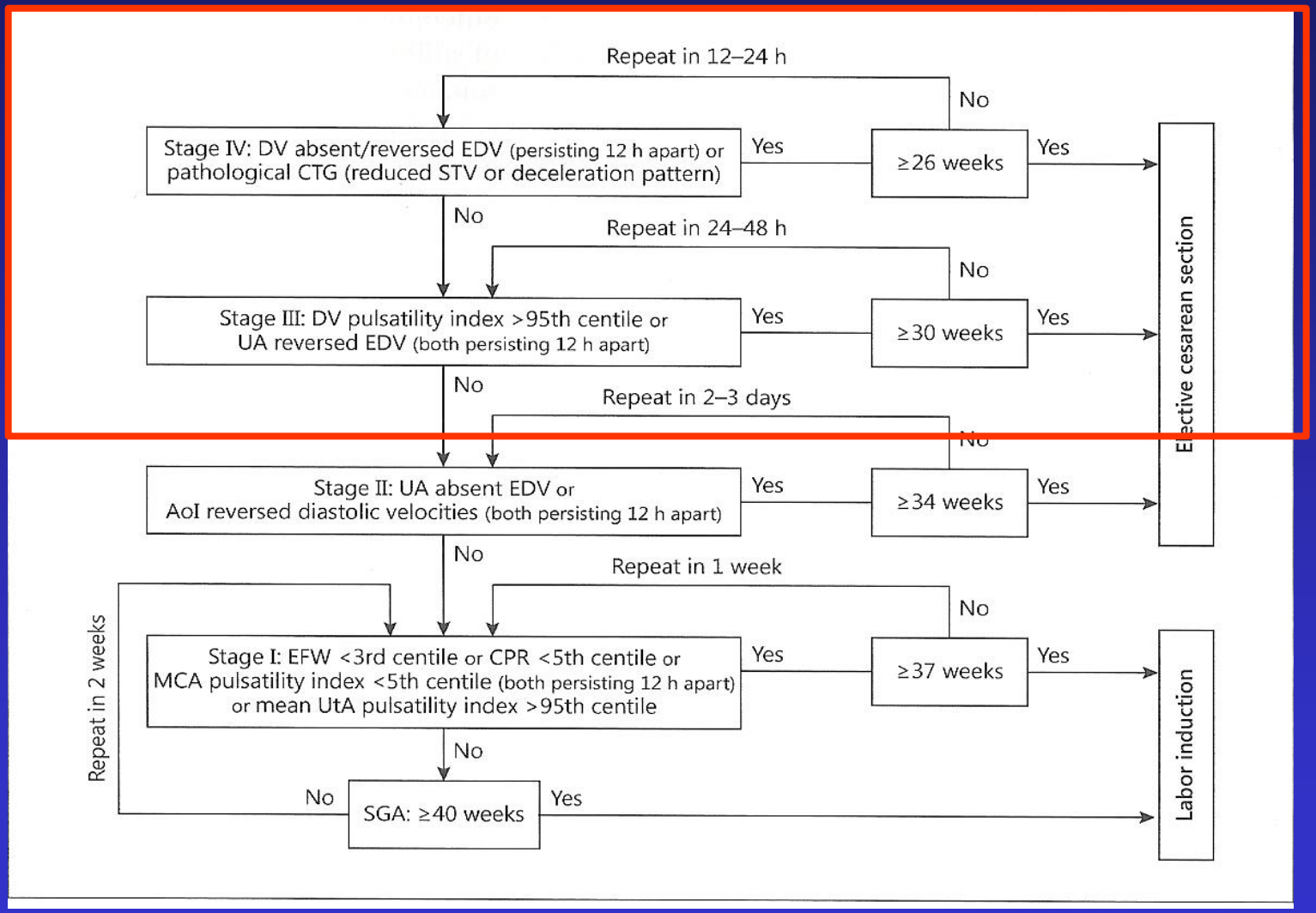






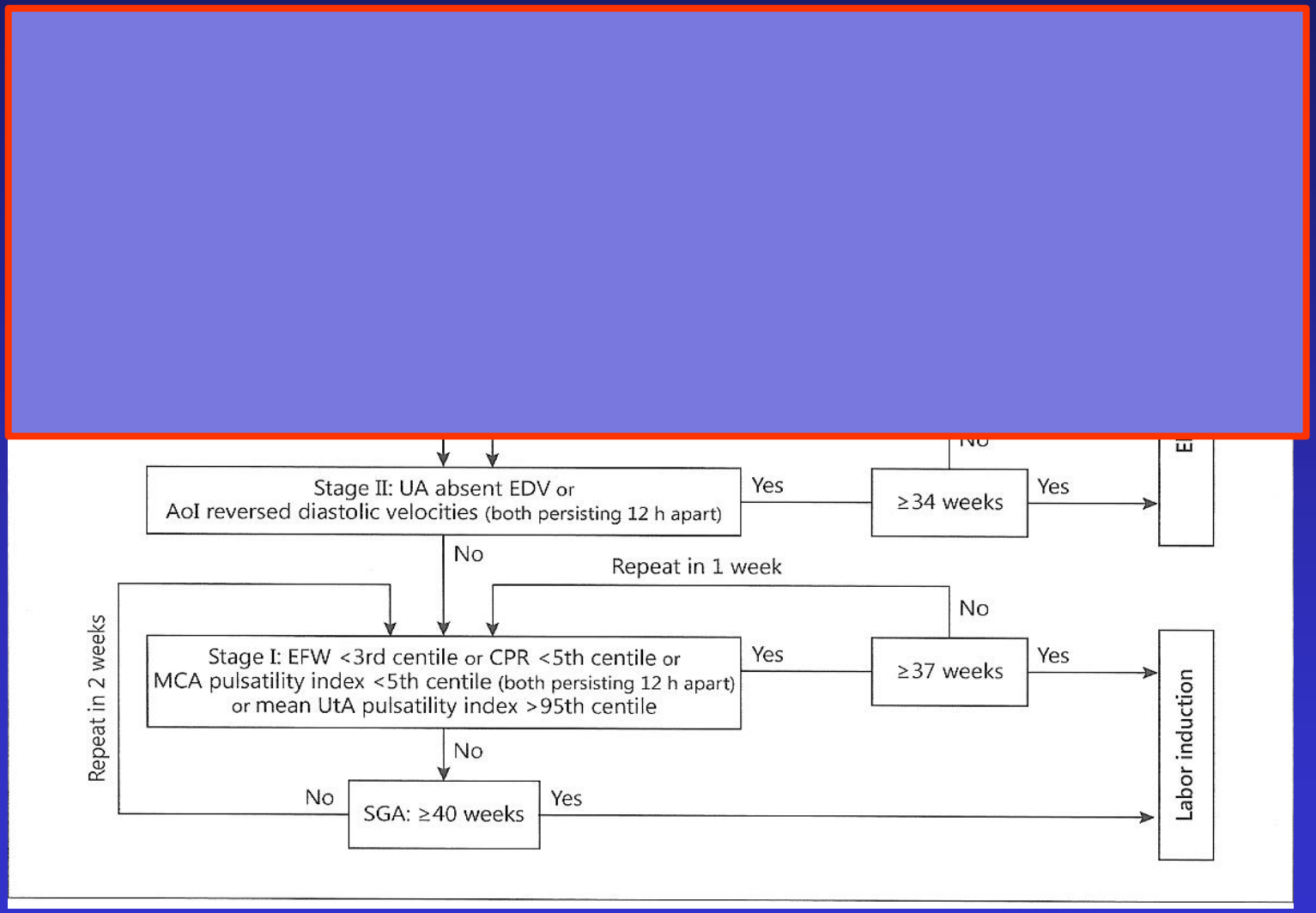
Graatsma et al ,JMFNM 2012

Decision algorithm for management of IUGR



Figueras & Gratacos, 2014

Decision algorithm for management of IUGR



Figueras & Gratacos, 2014

OSCAR 3

- Formal assessment of perinatal risk factors at 36 to 38 weeks
- With as the question: ‘take it out, or leave it in some what longer ’

And,……..

Neonatal encephalopathy in term infants: independent antenatal risk factors:

	Adjusted OR
- low socio-economic status	3.60
- neurol. diseases in family	2.73
- pregn. after infertility treatment	4.43
- maternal thyroid disease	9.70
- pregn. induced hypertension	6.30
- SFD <3rd centile	38.23
- SFD 3rd-9th centile	4.37
- antenatal haemorrhage	3.57
- viral infections during pregn.	2.97
- post term	13.2

(Badawi et al, 1999)

Term IUGR/SGA

Morbidity is most likely to be due to a combination of malnutrition and fetal hypoxia

Detection rate PE, with or without IUGR/ SGA

maternal characteristics, MAP, serum biomarkers

Screening test	Detection rate (95% confidence interval) for fixed FPR							
	Early Onset PE				Late Onset PE			
	All n= 68		with IUGR n=13		All n=99		with IUGR n=49	
	5%	10%	5%	10%	5%	10%	5%	10%
Maternal characteristics	40	56	39	69	22	31	27	41
Maternal characteristics plus								
PAPP-A	47	62	69	69	23	34	29	41
Free β-hCG	38	56	46	62	20	31	27	39
ADAM12	40	60	58	75	19	31	21	38
PlGF	51	58	67	75	22	35	34	53
MAP	50	64	39	62	27	45	24	41
Maternal characteristics plus combination of markers								
MAP and PAPP-A	53	71	69	69	32	46	32	41
MAP and PlGF	54	68	67	75	35	56	46	63
MAP, PAPP-A and PlGF	54	70	50	83	38	52	49	60
MAP, PAPP-A, ADAM12 and PlGF	56	72	67	92	40	49	49	57

Kuc et al PLOS One, 2013

High mortality/morbidity rate in the very small term babies

- Early identification is essential
  - Customized growth charts
  - Doppler uterine artery?
  - Umbilical/MCA Doppler ratio
  - Serial fetal growth measurements?
  - Measure of autonomic FHR control
  - Fetal movements !
  - Unlikely to be useful: serial AF assessment, FHR monitoring

First trimester markers

- Maternal history
- Maternal weight
- Maternal RR
- Uterine artery PI
- Maternal serum biomarkers

Metabolomics and late onset PE

TABLE 4

Prediction of late-onset preeclampsia based on logistic regression model (expanded dataset[a])

Model	Sensitivity, %	Specificity, %	AUC (95% CI)	*P* value
Glycerol[b]	40	94.1	0.79 (0.692–0.888)	< .001
Glycerol and weight[c]	40	95	0.796 (0.698–0.894)	< .001
Glycerol, 1-methylhistidine[d]	56.7	95	0.783 (0.667–0.898)	< .001

Respective probability equations based on the regression analyses.
AUC, area under curve; *CI*, confidence interval.

[a] Sixty normal cases added from prior publication[15] (total 30 late-onset preeclampsia and 119 normals); [b] Predictors considered in regression: glycerol, carnitine, and white/non-white race. Prob (preeclampsia) = 0.002*glycerol-2.60; [c] Predictors considered in regression: glycerol, carnitine, and weight. Prob (preeclampsia) = 0.002*glycerol + 0.033*weight; [d] Predictors considered in regression: glycerol, carnitine and 1-methylhistidine. Prob (preeclampsia) = 0.002*glycerol + 0.032*methylhistidine-4.04.

Bahado-Singh. Late-onset preeclampsia, metabolomics. Am J Obstet Gynecol 2013.

Remaining challenges

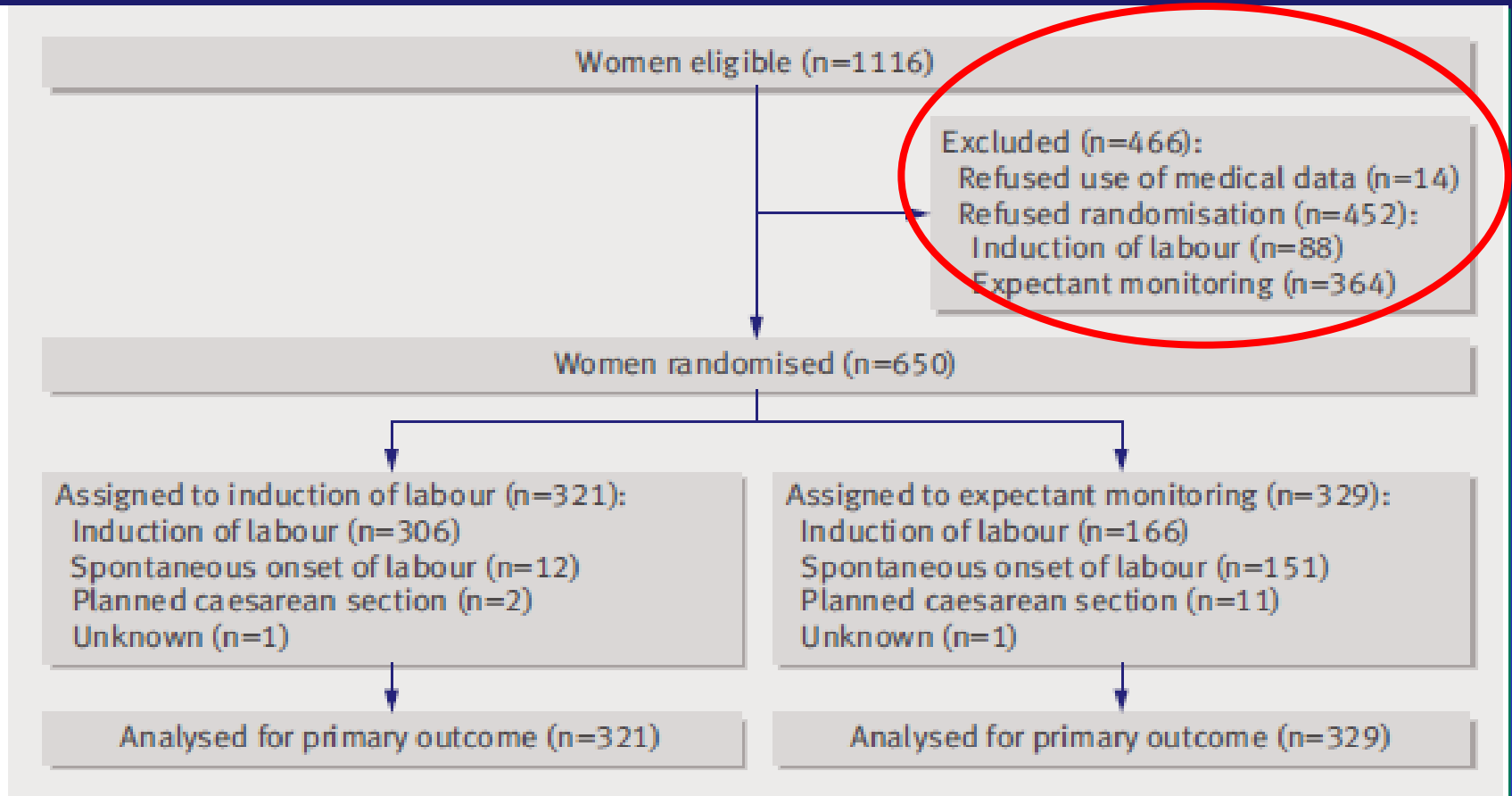
- To identify the small fetus at term
- To identify those small fetuses that are at risk for poor outcome, i.e. to discriminate between the SGA and IUGR fetus
- Realizing that small may be everywhere below the 50th centile

SAFARI study; N of inclusions: 500

- Primary outcome:
- Antepartum intervention for fetal distress
- Perinatal mortality
- pH umb art < 7.05
- Apgarscore 5 min < 7
- Admission Nicu
- 8% of cases*, n=40, 4 antenatal items to be tested
- Cerebro-placental (MCA/Umb A) ratio
- PI ut artery
- Head circumference/brain volume
- Index autonomic FHR control

*Digitat study

DIGITAT study



Flow diagram of the trial process

Weight at 1 y of age in relation to death due to cardiovascular disease <65 y

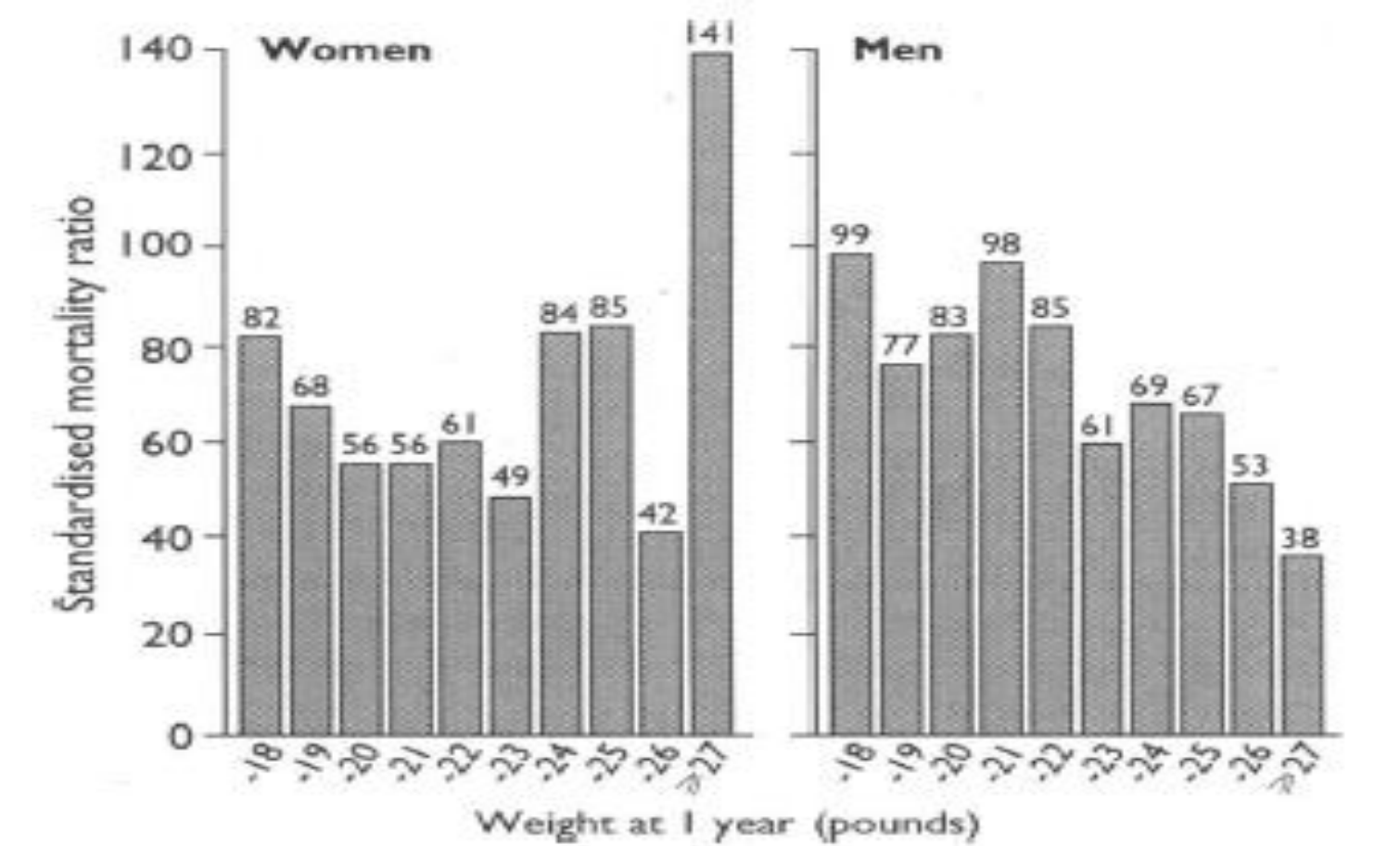


FIG 2—*Standardised mortality ratios for cardiovascular disease below age of 65 according to weight at 1 year*

Osmond et al, BMJ 1993

Optimal fetal growth

- Most intrauterine deaths occur in fetuses with a weight in the so-called normal range
- When developing risk scores for IUFD, including maternal age, social class, BMI and fetal weight not only weights below the 10^{th} centile should be included, but a graded more sophisticated centile distribution

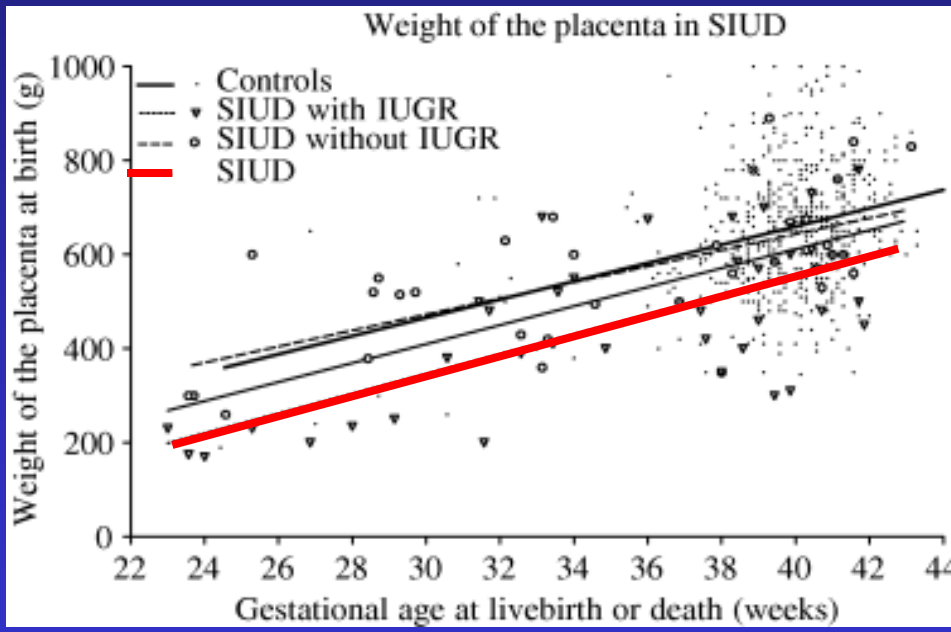

Thank you

Term IUGR/ SFD

-Half of unexplained stillbirths occur > 37 wks

-50-65% of unexpl stillbirths are (customised) IUGR,

and have a small placenta:



-In >60% of all stillbirths significant placental or cord pathology is present

Froen et al,2001 & 2004;Gardosi et al,2005;Horn et al,2004

CS and neonatal hospitalization in term infants with an estimated fetal weight <3rd centile

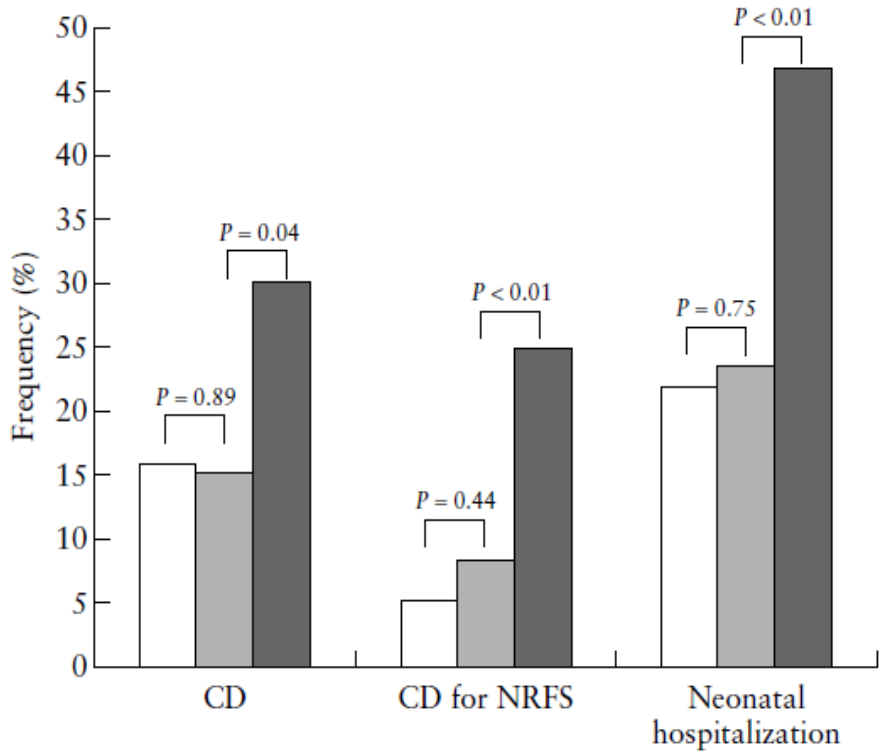


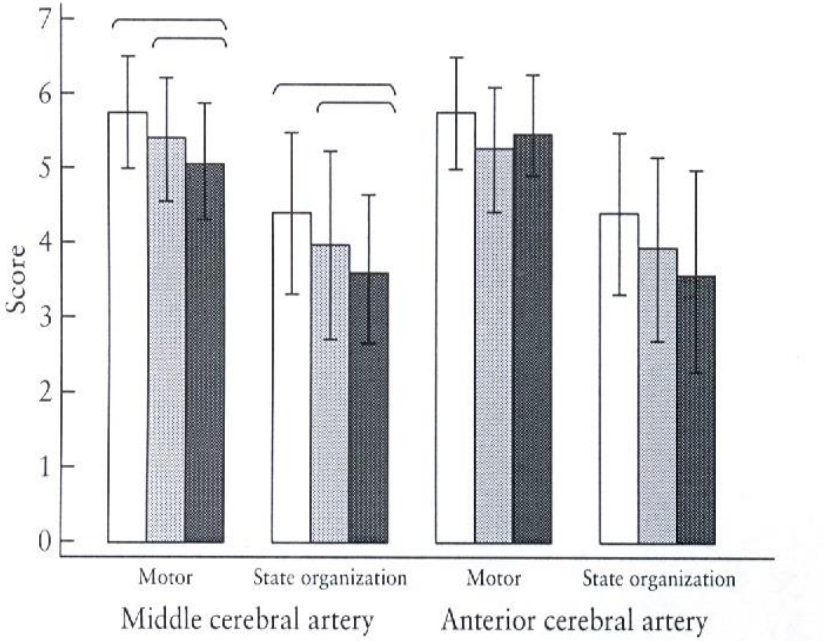
Figure 1 Frequency of intrapartum Cesarean delivery (CD), emergency CD due to non-reassuring fetal status (NRFS) and any period of neonatal hospitalization for controls and for small-for-gestational-age fetuses classified according to estimated fetal weight centile group. □, Controls; ▒, SGA ≥3rd centile; ■, SGA < 3rd centile.

-132 SGA,(with normal Dopplers)
-60 with EFW <3rd centile
-132 controls

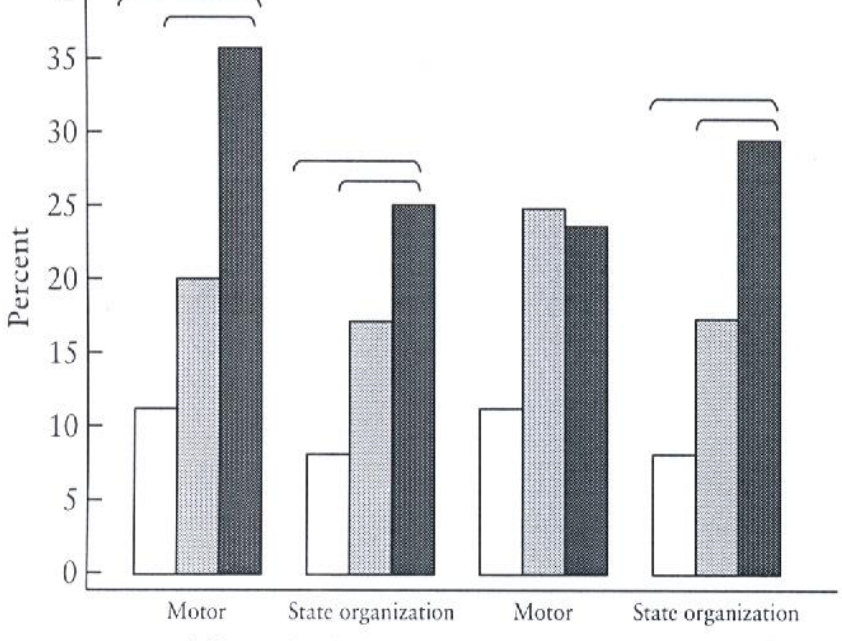
Savchev et al, UOG 2012

Neonatal neurobehavior in term AGA and SGA infants without and with prenatal redistribution

Neurobehavioral scores

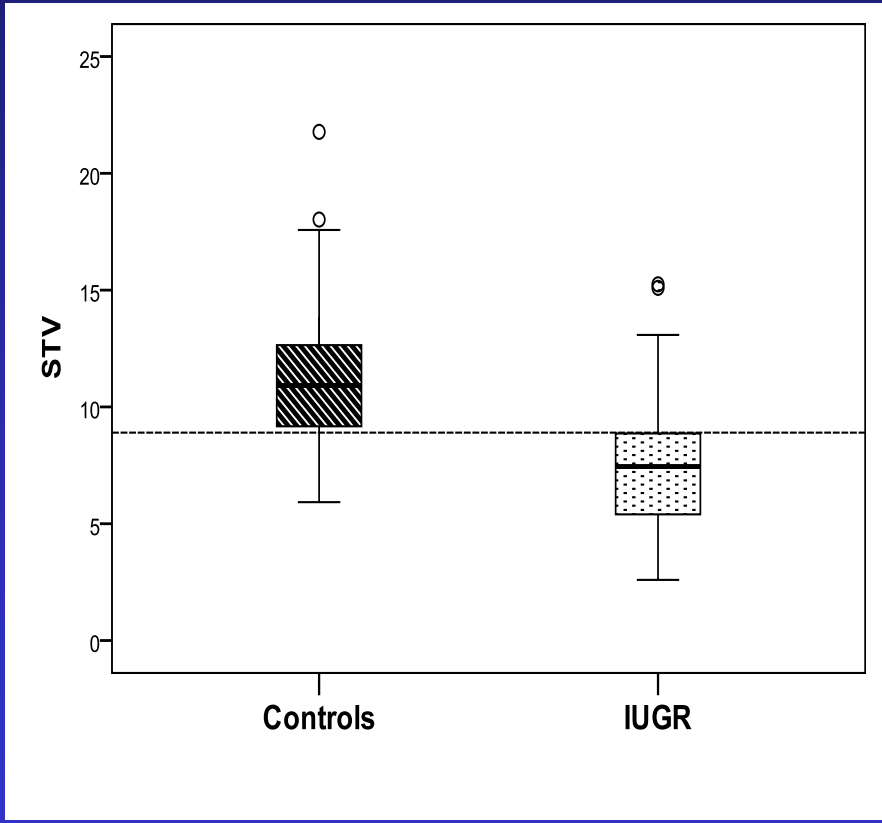


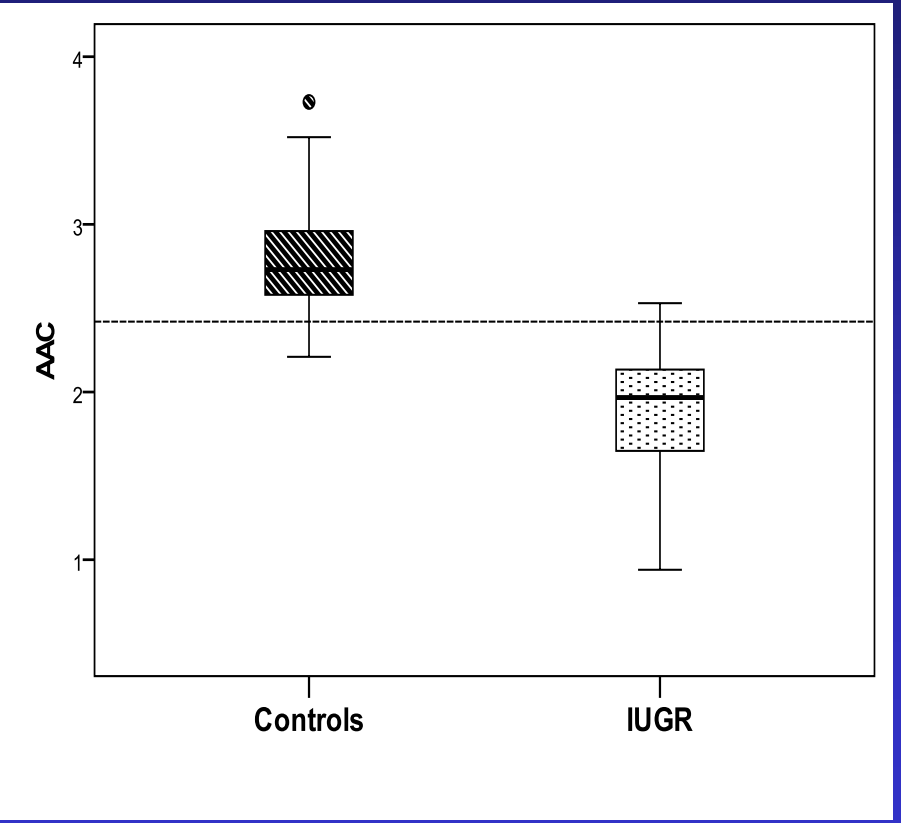
% abnormal neurobehavior



Oros et al, UOG, 2010

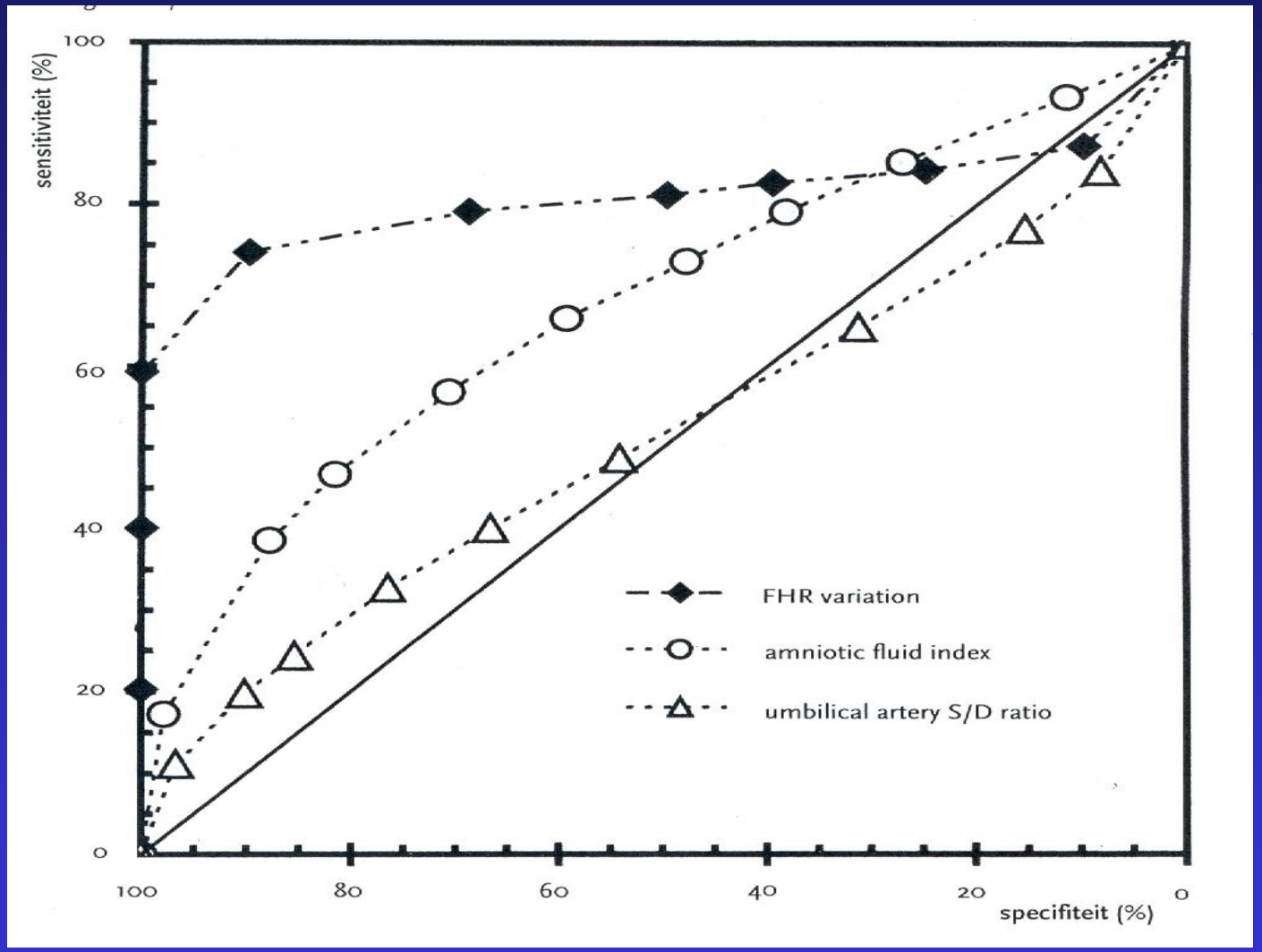
STV and Average Acceleration capacity in controls and IUGR





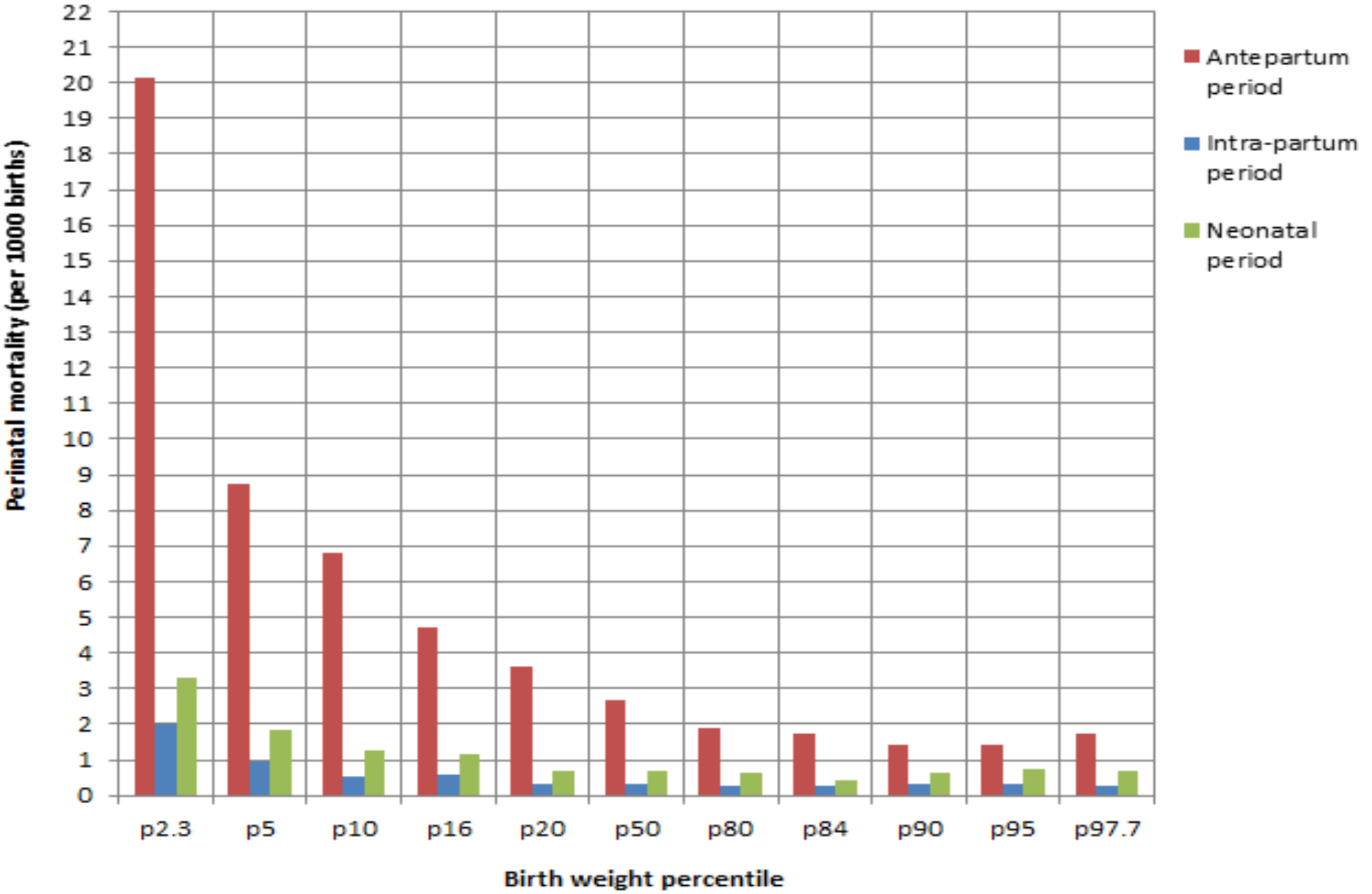
Lobmaier et al, 2010

FHR, Amniotic fluid and Doppler Umb art, 41 wks



N=367, Weiner et al, AJOG, 1994

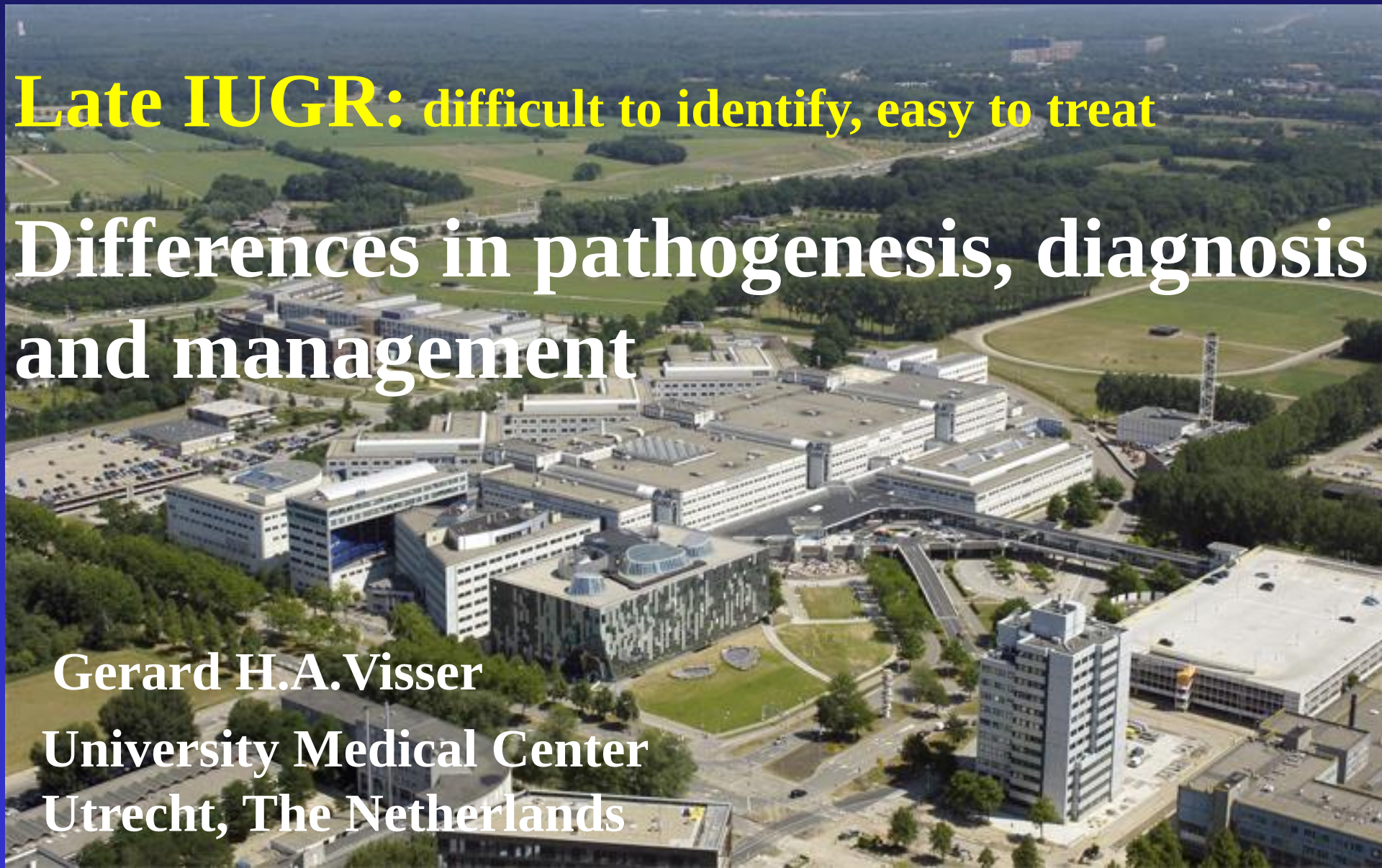
Perinatal mortality>28 wks



Early IUGR: easy to identify, difficult to treat

Late IUGR: difficult to identify, easy to treat

Differences in pathogenesis, diagnosis and management



Gerard H.A.Visser

University Medical Center
Utrecht, The Netherlands

So, ……

- Easy identification
- Sufficient monitoring tools

- But,….. what next??
- Therapy: Oxygen?
  Corticosteroids?
  Neuroprevention ($MgSO_4$, Allopurinol)

So, ……

- Easy identification
- Sufficient monitoring tools

- But,….. what next??
- So, only option is (timing of) delivery (GRIT study*, TRUFFLE study)

Thornton et al Lancet 2004, Walker et al AJOG 2011

Single center cohort study:

IUGR,<34 wks, Univ. Med Center Utrecht, n=180

Variables

Gestational age
Birth weight
parity
Sex
Maternal disease
Corticosteroids
FHR pattern
Umbilical artery PI
Ductus Venosus
Apgar and pH at birth
Placenta histology
IVH/ROP/NEC/RDS/NICU days
Neonatal cranial ultrasound
Neurological examination at term age
Neurodevelopment at 2 years

outcome

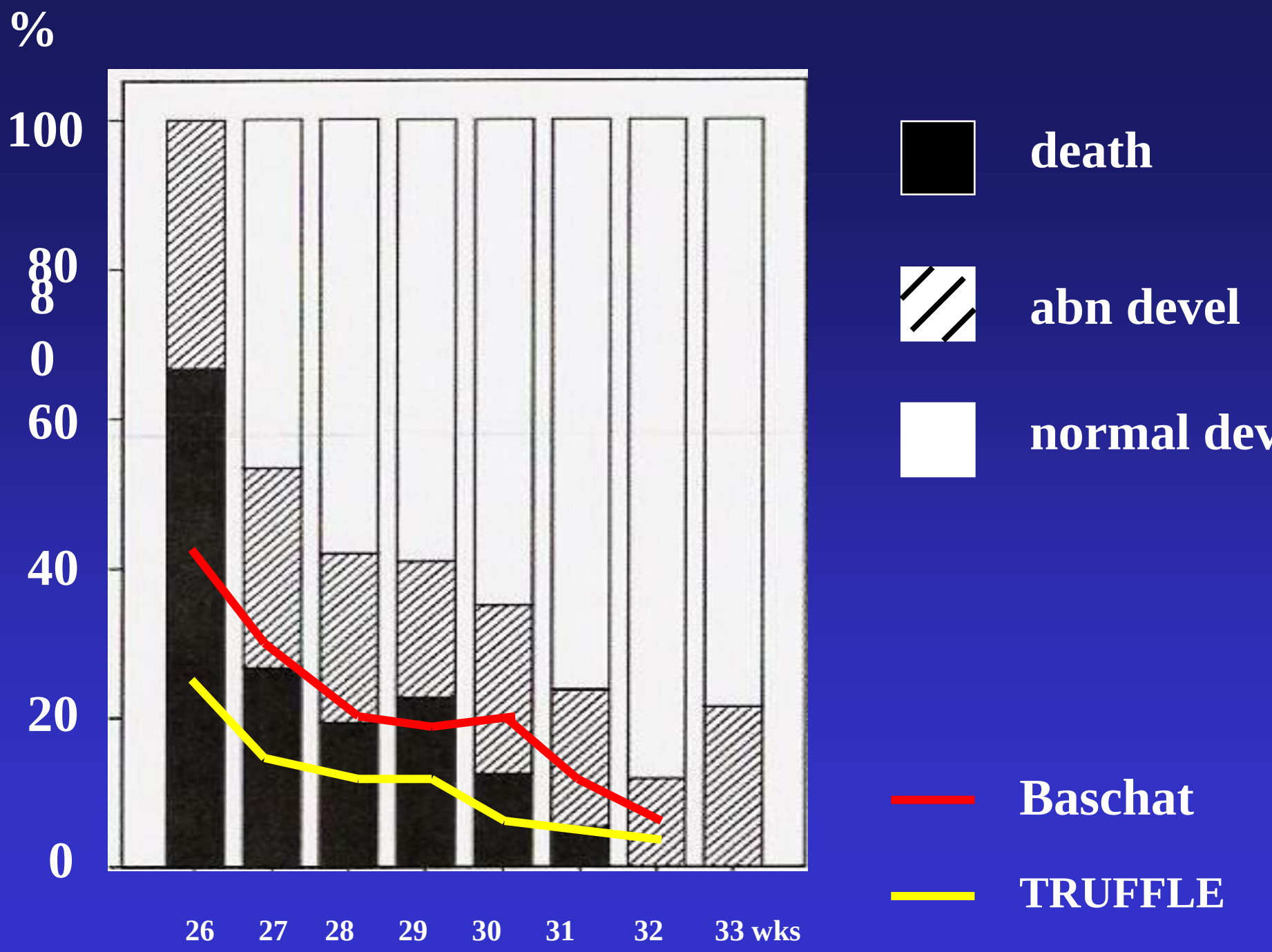
Neonatal mortality

Infant mortality

Neonatal morbidity

Neur.morbidity at 2 years

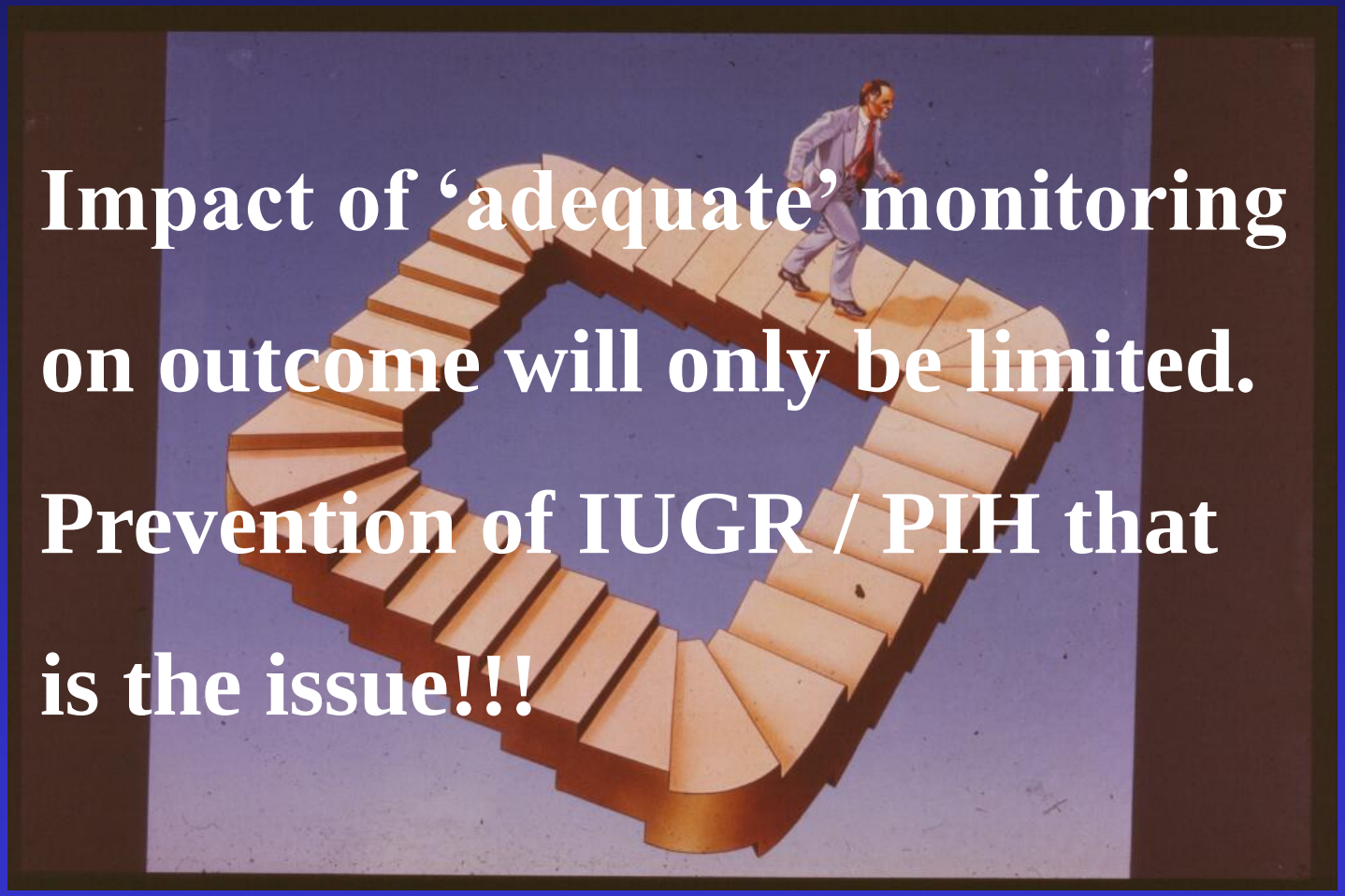
Torrance et al, UOG, 2010


%
100
80
8
0
60
40
20
0
26
27
28
29
30
31
32
33 wks
death
abn devel
normal dev
Baschat
TRUFFLE

Brain damage in the early IUGR fetus

- is it due to hypoxaemia,
- to chronic malnutrition
- or to both

All in all,



Impact of ‘adequate’ monitoring on outcome will only be limited. Prevention of IUGR / PIH that is the issue!!!

Prevention of PE with aspirin

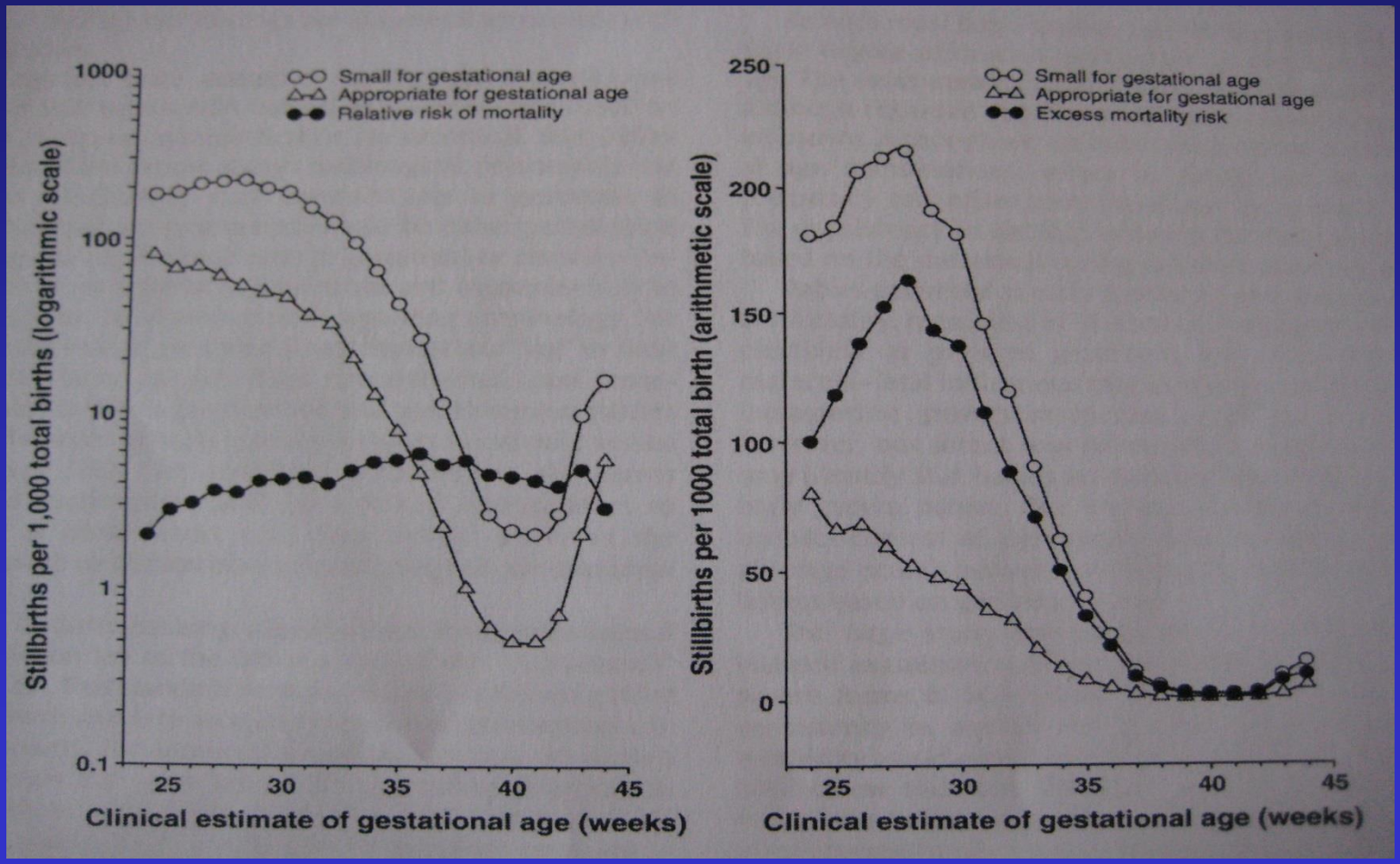
- Meta-analysis, 31 RCTs 32.217 patients, PE 0.90 (95% CI 0.84-0.97); Askie, Lancet 2007

- Metanalysis 27 RCTs 11.348 patients, early-late start of Aspirin (Bujold et al 2010):
- =< 16 wks RR 0.47 (CI 0.34-0.65) IUGR RR 0.44 (CI 0.30-0.65)

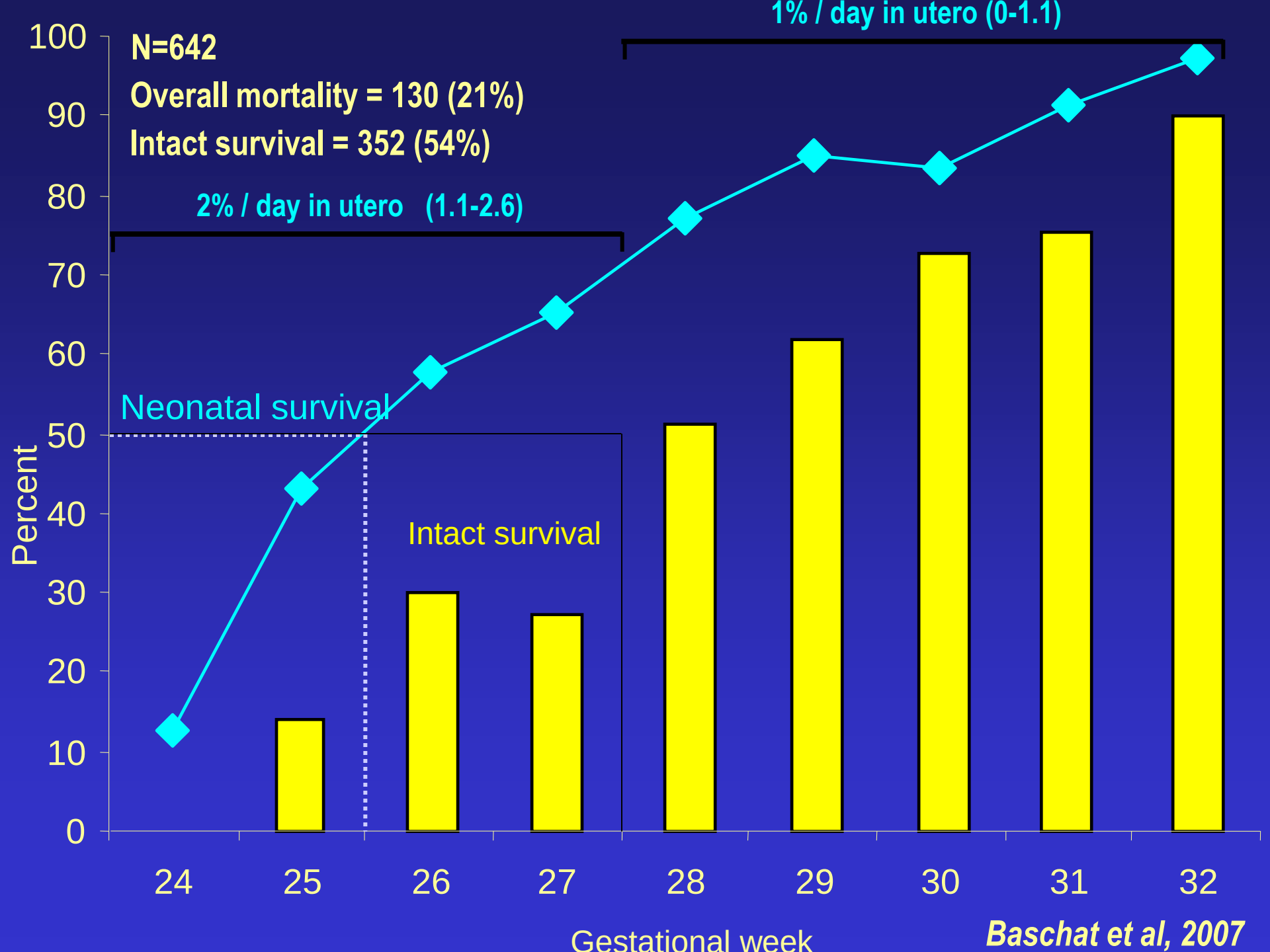
- > 16 wks RR 0.81 ns IUGR RR 0.98 ns

- Especially for severe PE (RR 0.09), preterm birth (RR 0.22)

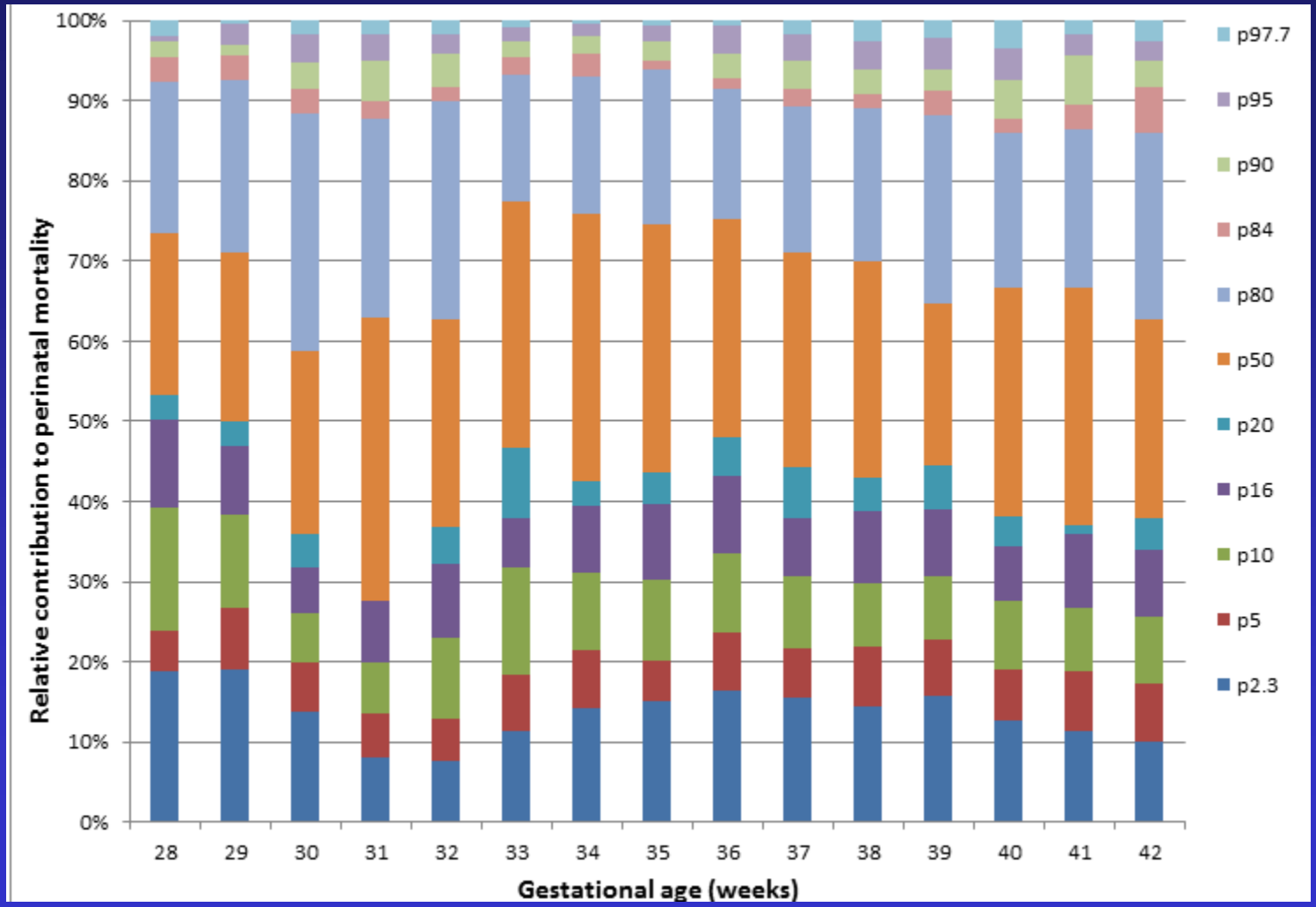
Pathological or constitutional SGA and stillbirth rate



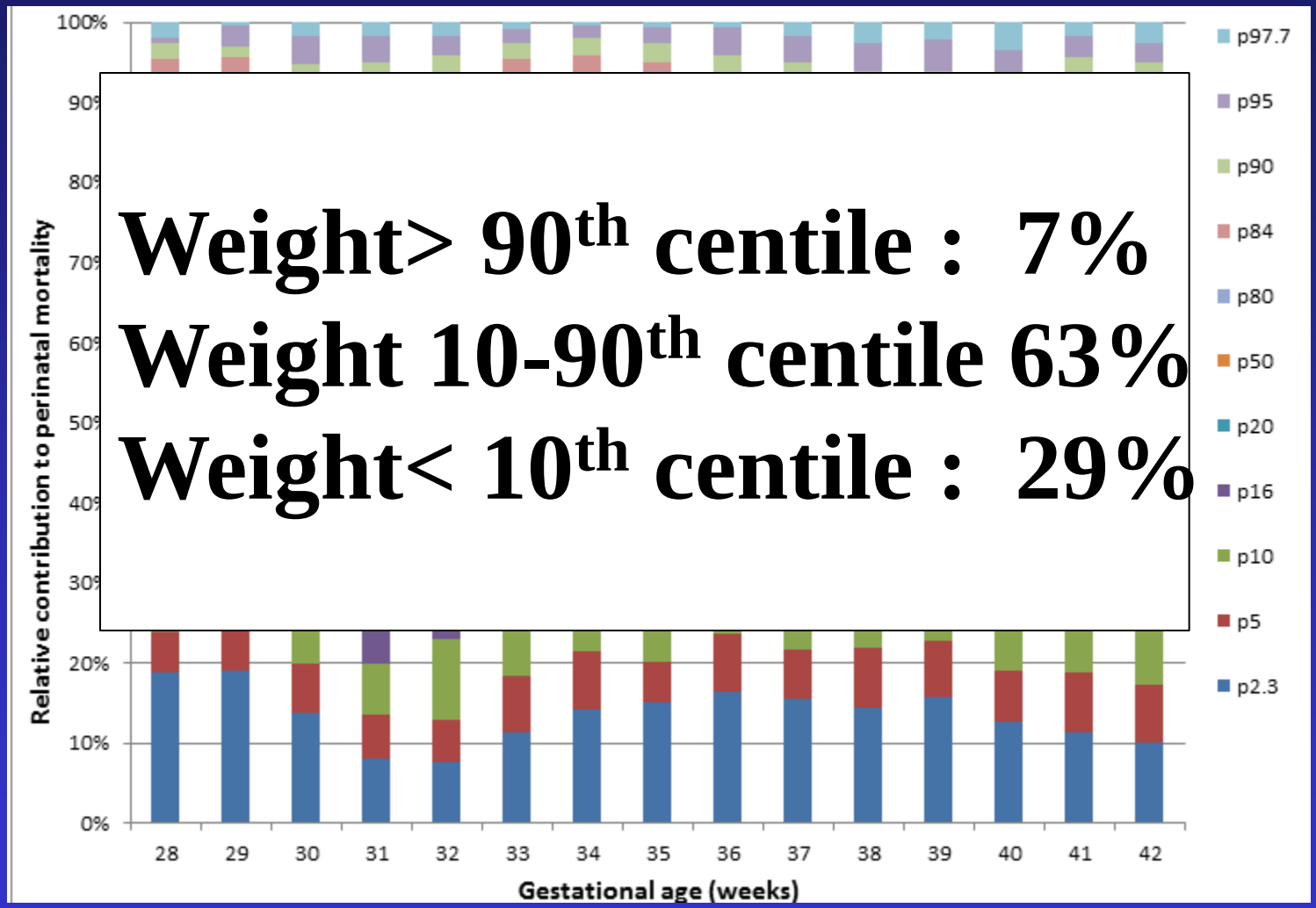
Ananth & Vintzileos, EHD, 2009; USA1995-2004, n>19 million non-malformed infants


N=642
Overall mortality = 130 (21%)
Intact survival = 352 (54%)
2% / day in utero (1.1-2.6)
1% / day in utero (0-1.1)
Neonatal survival
Intact survival
Percent
100
90
80
70
60
50
40
30
20
10
0
24
25
26
27
28
29
30
31
32
Gestational week
Baschat et al, 2007

Contribution of the different birt weight centile groups to perinatal mortality



Contribution of the different birt weight centile groups to perinatal mortality



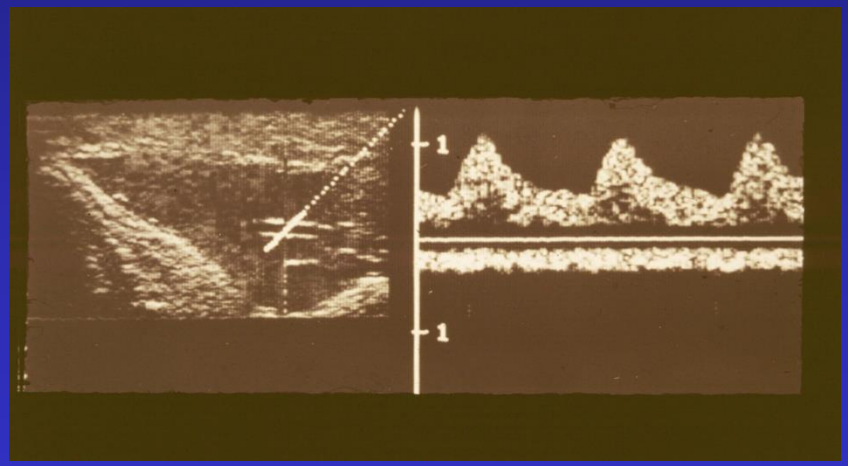
Customized assessment of growth

- Charts based on optimal fetal weight at term
- Taking into account:
  - maternal height
  - weight in early pregnancy
  - ethnic origin
  - parity
- Exclusion of factors that effect optimal growth (e.g. smoking)

(Gardosi et al, 2005)

Early IUGR

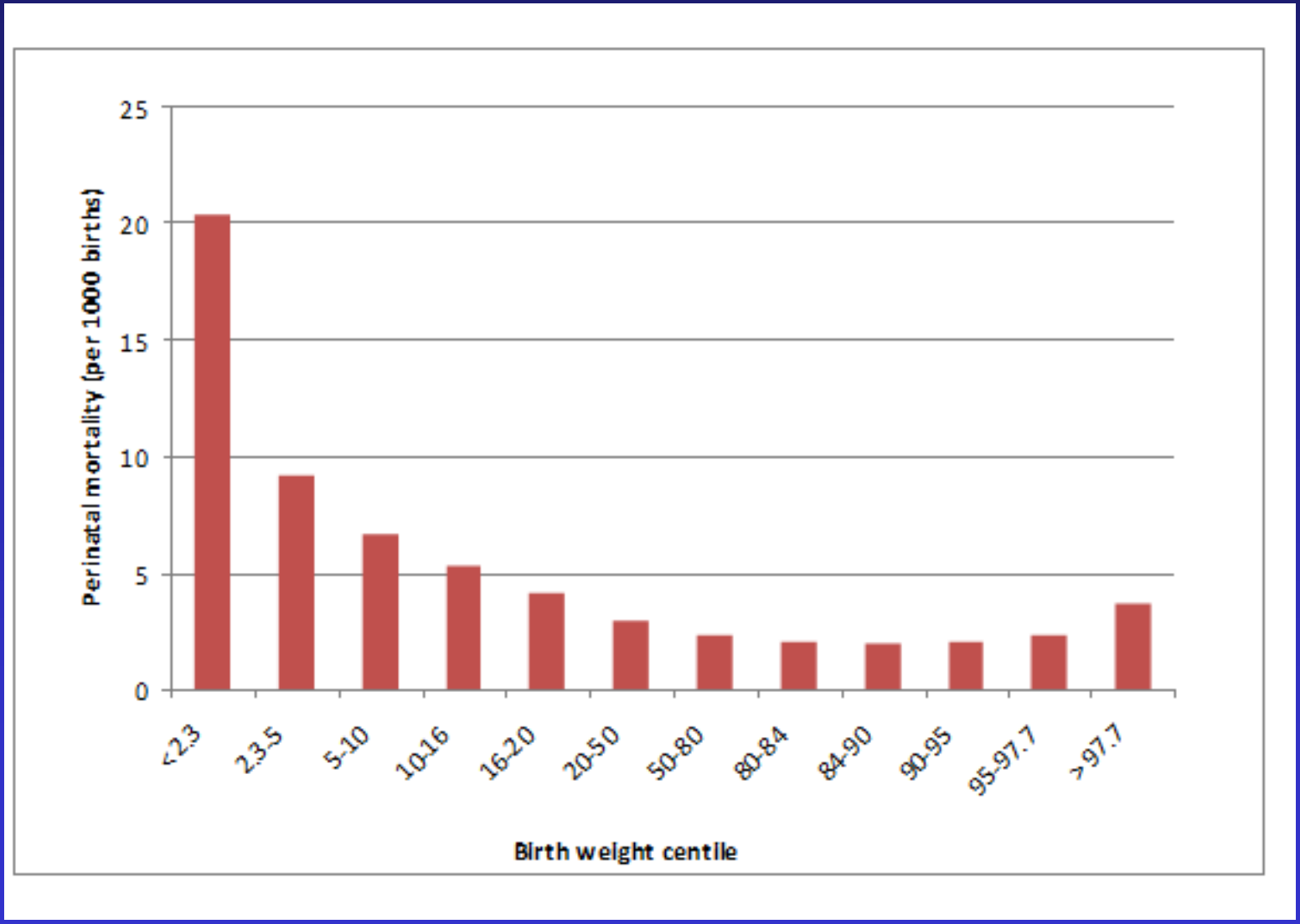
Definition: SGA with abnormal Doppler umbilical artery



Abormal Dopplers in umbilical artery only occur in case of a 30 to 50 % reduction in placental capacity/function

Perinatal mortality >28 wks, Nlds 2000-2008

After correction for possible IUD < 28 weeks; Vasak et al, unpublished data

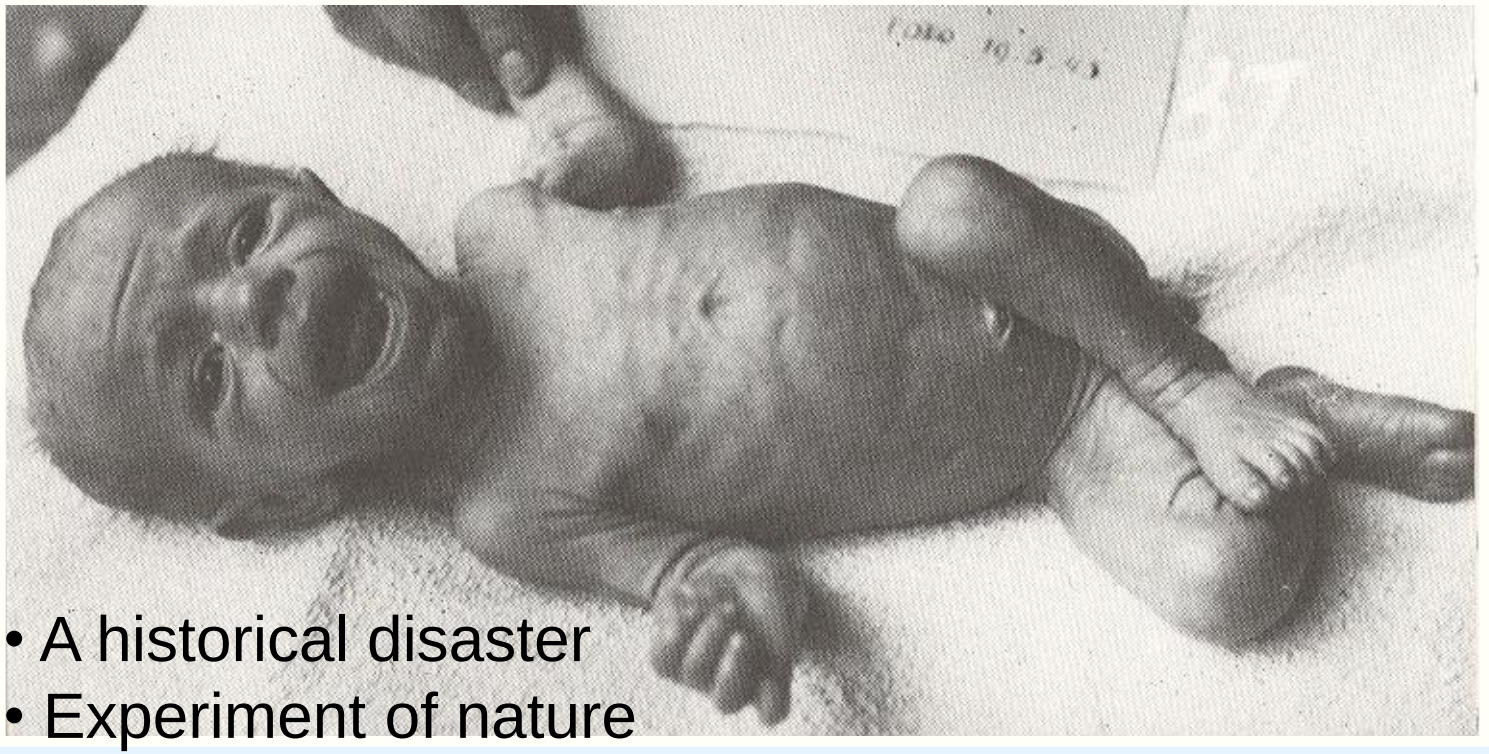


Beyond Birth Weight

- The Dutch Experience:

- The Dutch Famine
- Optimal fetal growth

Outcome after the Dutch Hunger Winter



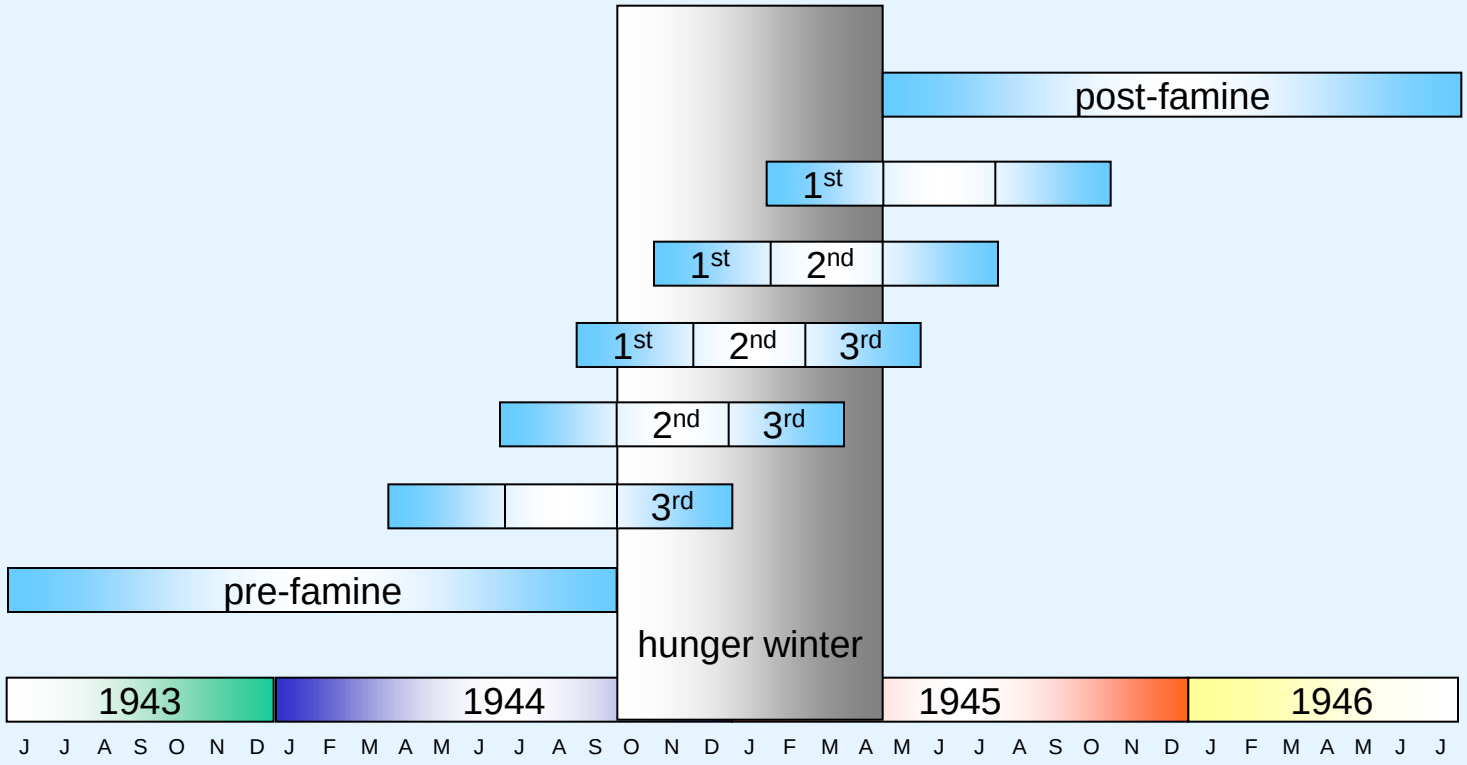
- A historical disaster
- Experiment of nature

To keep the stove burning…….

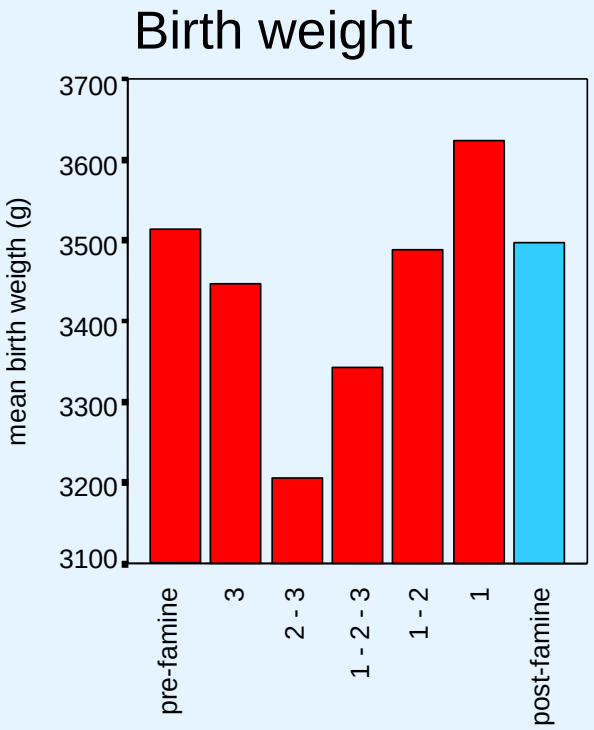
Voorburg

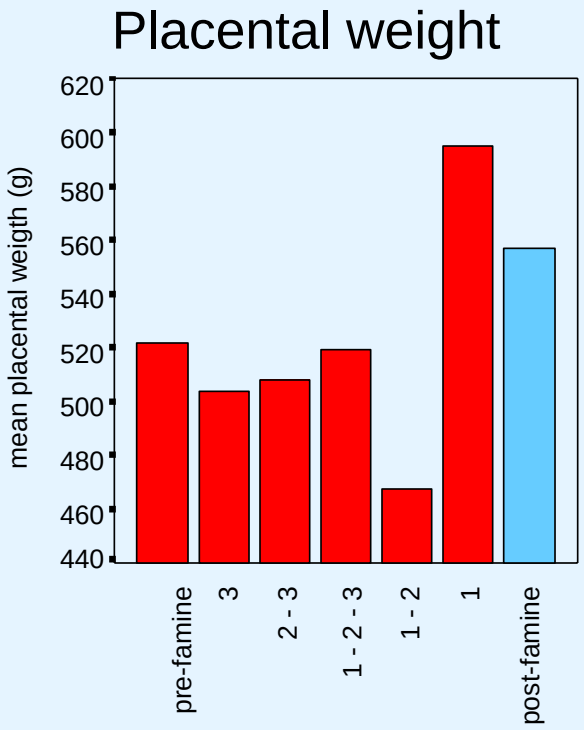
Amsterdam

7 famine exposure groups



Birth weight and placental weight
according to famine exposure





Exposure

	Early	Mid	Late
Young adult			
• cong. neural def.	+		
• ♂ obese	+		
40-60 years			
• brain anomalies	+		
• schizophrenia	+		
• antisocial person.dis	+		
• major affective disorder			+
• depressive symptoms	+	+	
• ↓ perceived mental health	+	+	
• ♀ obese	+		+
• atherogenic lipid profile	+ (?)		
• BP ↑ low protein %			+
• BP ↑ after stress	+		
• coronary heart disease	+		
• impaired glucose tolerance	+	+	+(?)
• micro albuminuria		+	

Or: why is human fetal growth is restrained below optimal for fetal survival?

Because the evolution of the large head, and changes in pelvic dimensions and orientation in association with bipedalism

constitute a major challenge for vaginal delivery*

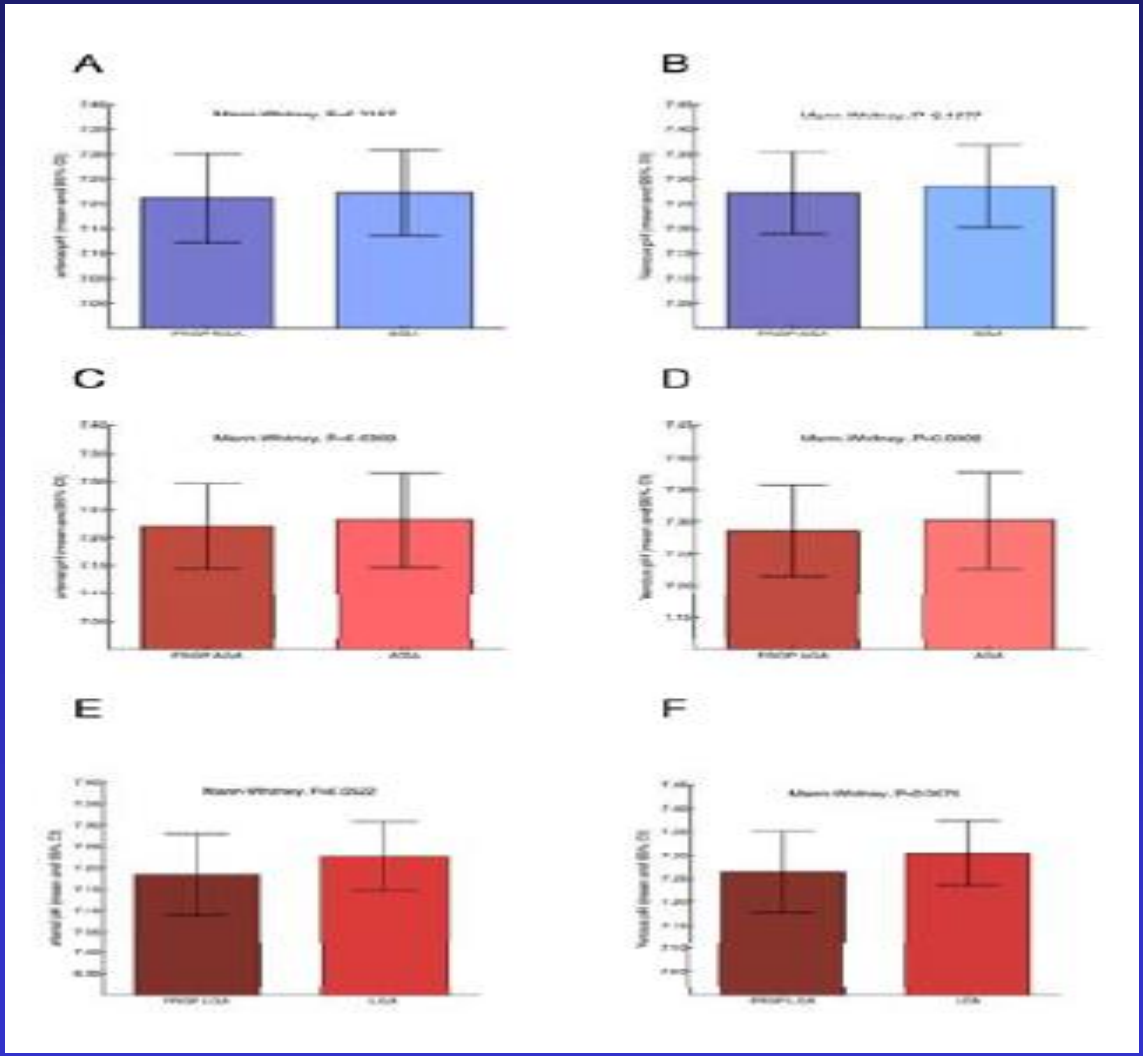
*Trevathan et al, Evolutionary Medicine 189, 1999

Optimal timing of delivery of early IUGR

First occurrence of abnormal FHR or Ductus venosus patterns

TRUFFLE study, Lees et al, Lancet 2015

Redistribution and art and venous cord pH



SGA

AGA

LGA

art pH

ven pH

Morales-Rosello et al, 2014

IUGR and/or low birth weight

low birth weight

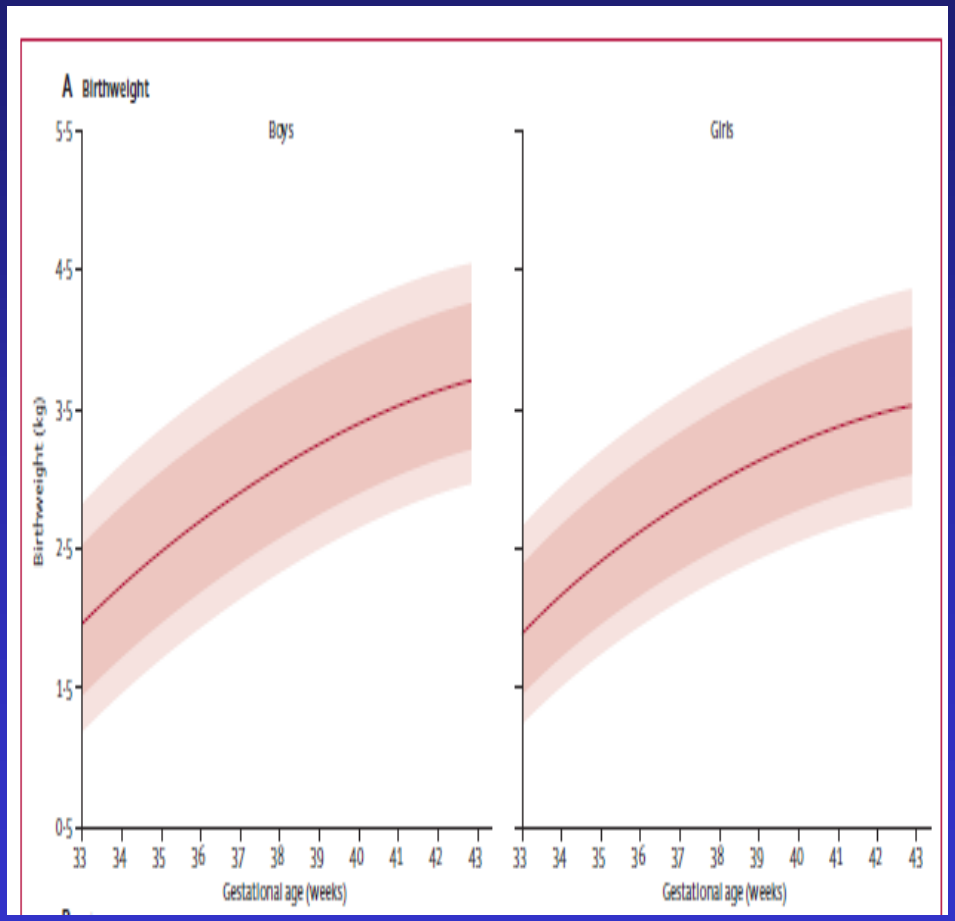
Preterm	IUGR	SGA
Gestational Age	placental capacity	pop. based birth weight centiles

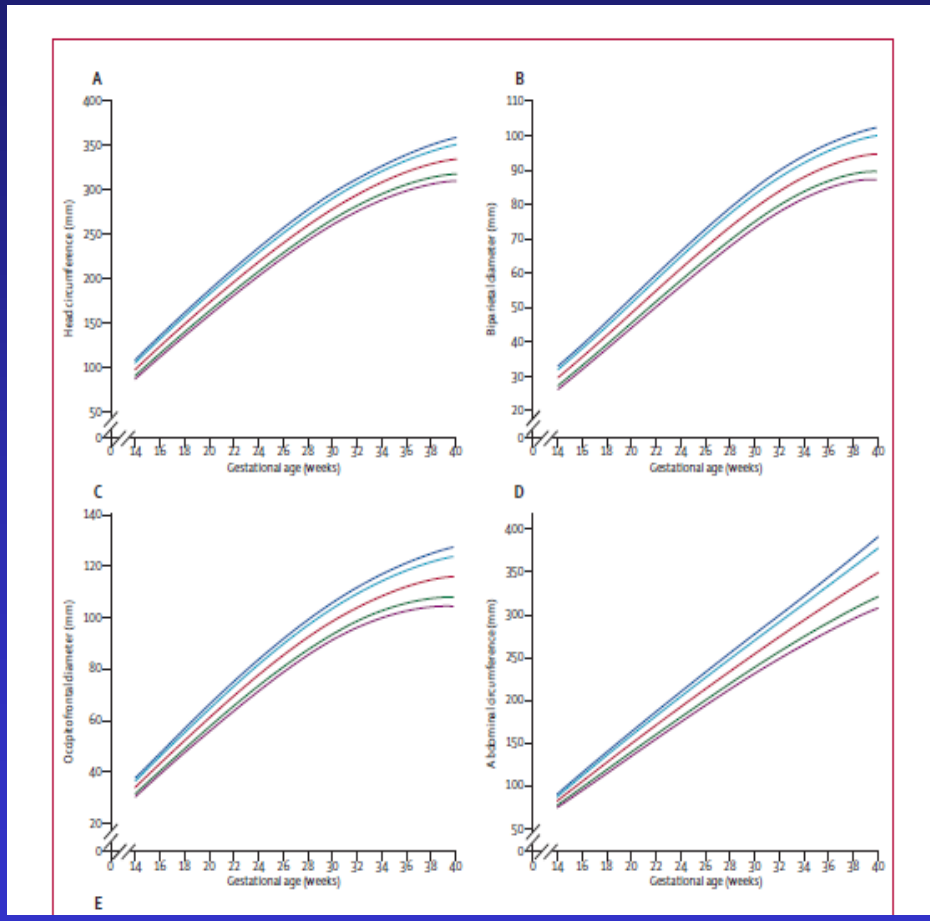
SGA customized versus population

"Better identification of fetuses at risk of stillbirth and neonatal death, probably due to improved identification of fetal growth restriction"

(Clausson et al, BJOG 2001; 108: 830-834)

Intergrowth-21: birth weight and ultrasound sizes for age





Villar et al and Papageorghiou et al, Lancet 2014

Discussion…….

We believe these standards, as opposed to the several locally produced references in use worldwide,[4] have the potential to improve pregnancy outcomes,[44] not least because at present the diagnosis of fetal growth restriction is made at different levels of care, even within the same regions or countries, using different fetal growth charts and cutoff points—ie, fetuses can be classified as growth restricted in one part of a city or country and of healthy size in another. This leads to inaccuracy in diagnosis and ultimately unnecessary, or an absence of, appropriate interventions. Additionally,

use of fetal growth standards derived from a healthy population reduces the risk of underdiagnosing fetal growth restriction, which can occur when the fetus is monitored against references that include high-risk mothers (panel).

..but may well increase the risk of overdiagnosing…..

Papageorghiou et al, Lancet 2014

Discussion…….

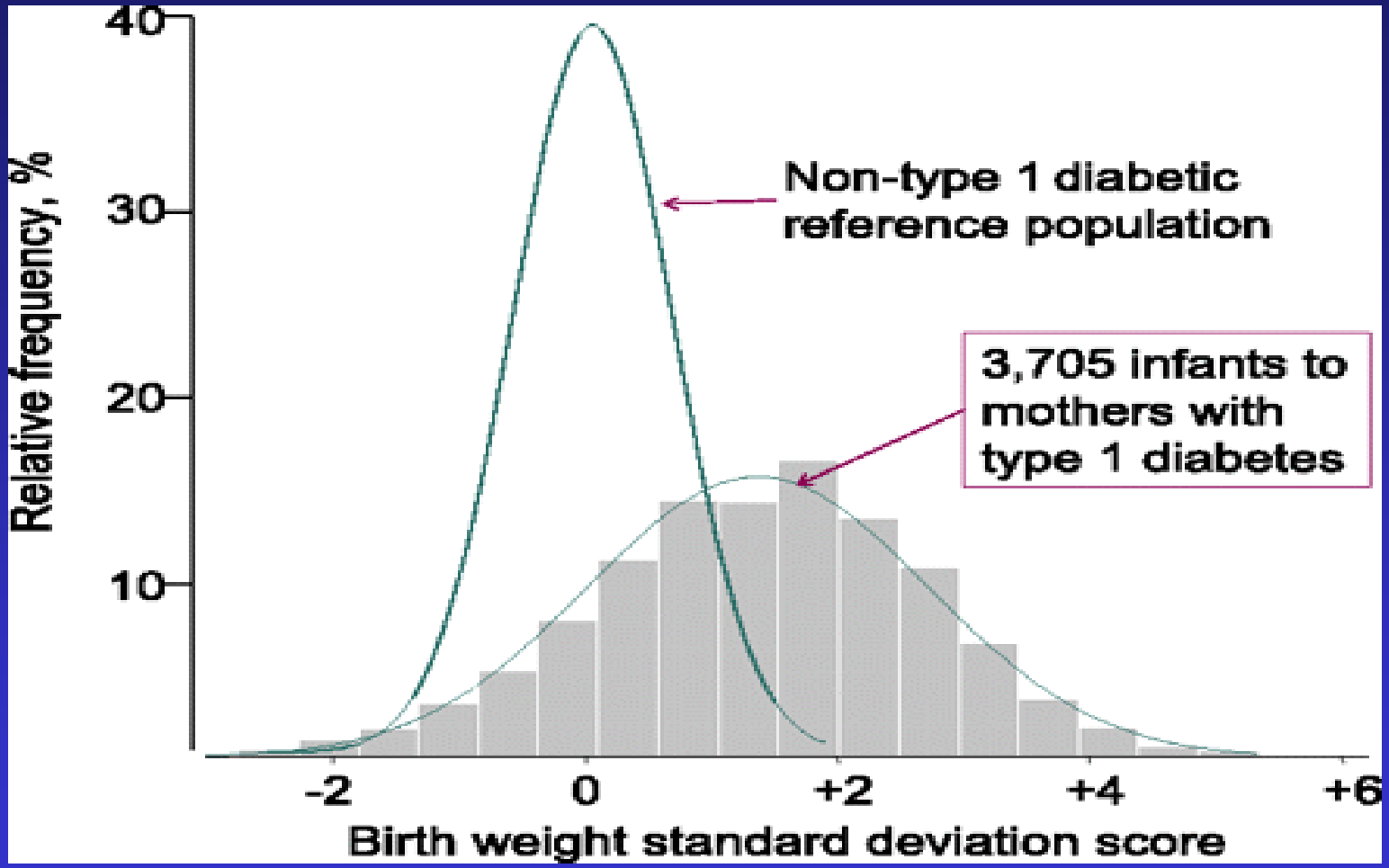
We believe these standards, as opposed to the several locally produced references in use worldwide,[4] have the

Can we diagnose fetal growth restriction from ultrasound fetal size charts?
Does the 10-90th centile range indicates normality?

growth restriction, which can occur when the fetus is monitored against references that include high-risk mothers (panel).

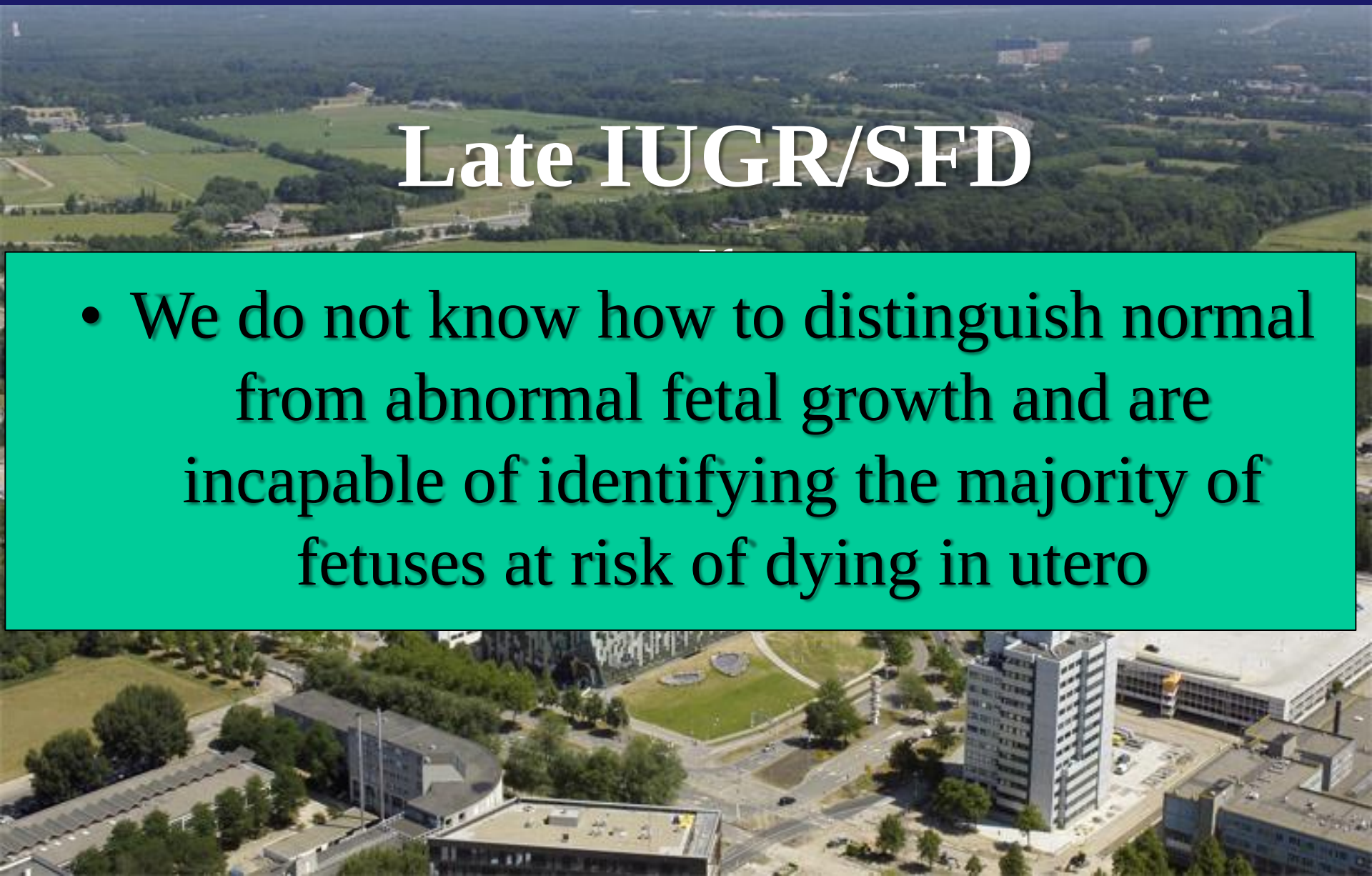
Papageorghiou et al, Lancet 2014

Birth weight distribution



Persson et al. Diab Care 2011;34:1145-1149

University Medical Center, Utrecht, the NL



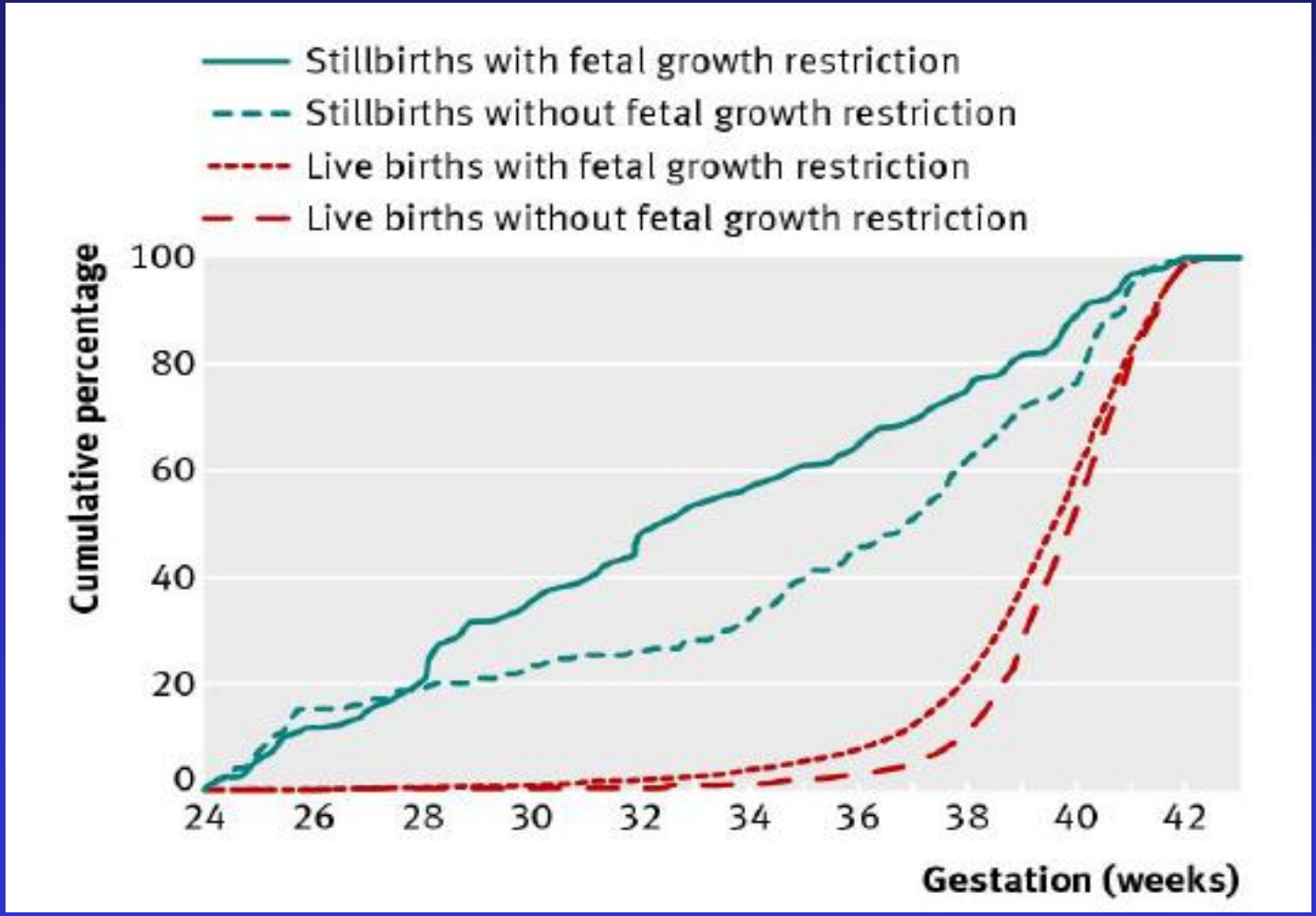
Late IUGR/SFD

- We do not know how to distinguish normal from abnormal fetal growth and are incapable of identifying the majority of fetuses at risk of dying in utero

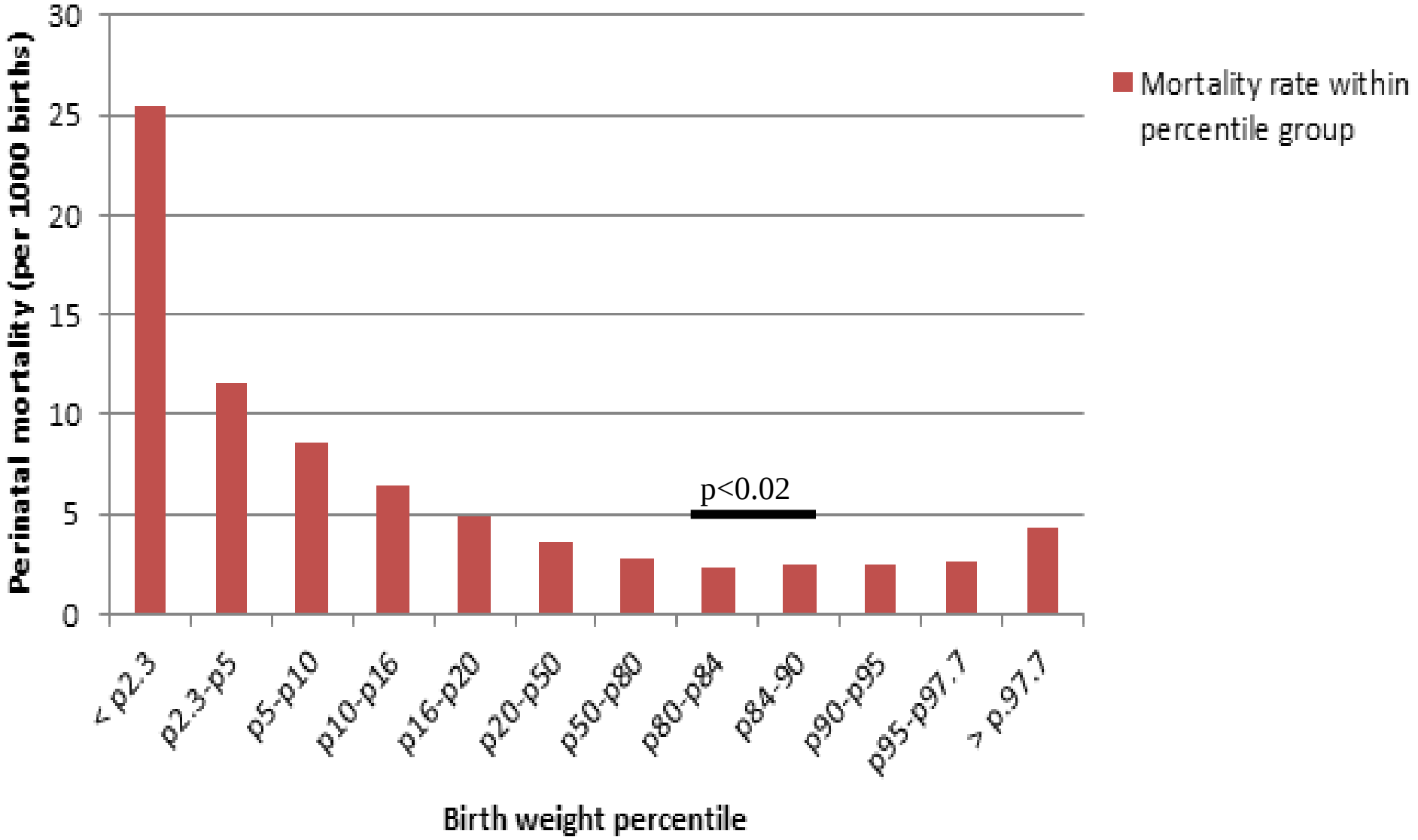
So, for short and long term survival

- Your birth weight should be around the 90th centile
- And that also holds for weight at 1-2 y of age

Or: why is human fetal growth restrained below optimal for fetal survival?


Stillbirths with fetal growth restriction
Stillbirths without fetal growth restriction
Live births with fetal growth restriction
Live births without fetal growth restriction
Cumulative percentage
100
80
60
40
20
0
24
26
28
30
32
34
36
38
40
42
Gestation (weeks)

Perinatal mortality >28 wks, Nlds 2000-2008



Smoking, stillbirth and BW centiles;

OR; multivariable analysis (Moriatis et al, 2014)

BW centile		smokers	non-smokers
• 1-3		5.5	10.5
• 4-10		2.4	3.8
• 11-20		1.4	1.9
• 21-80	reference		
• 80-90		1.0	0.8
• 90-97		1.3	0.6
• >97		4.7	1.8
• Overall		1.6 (1.4-1.8)	