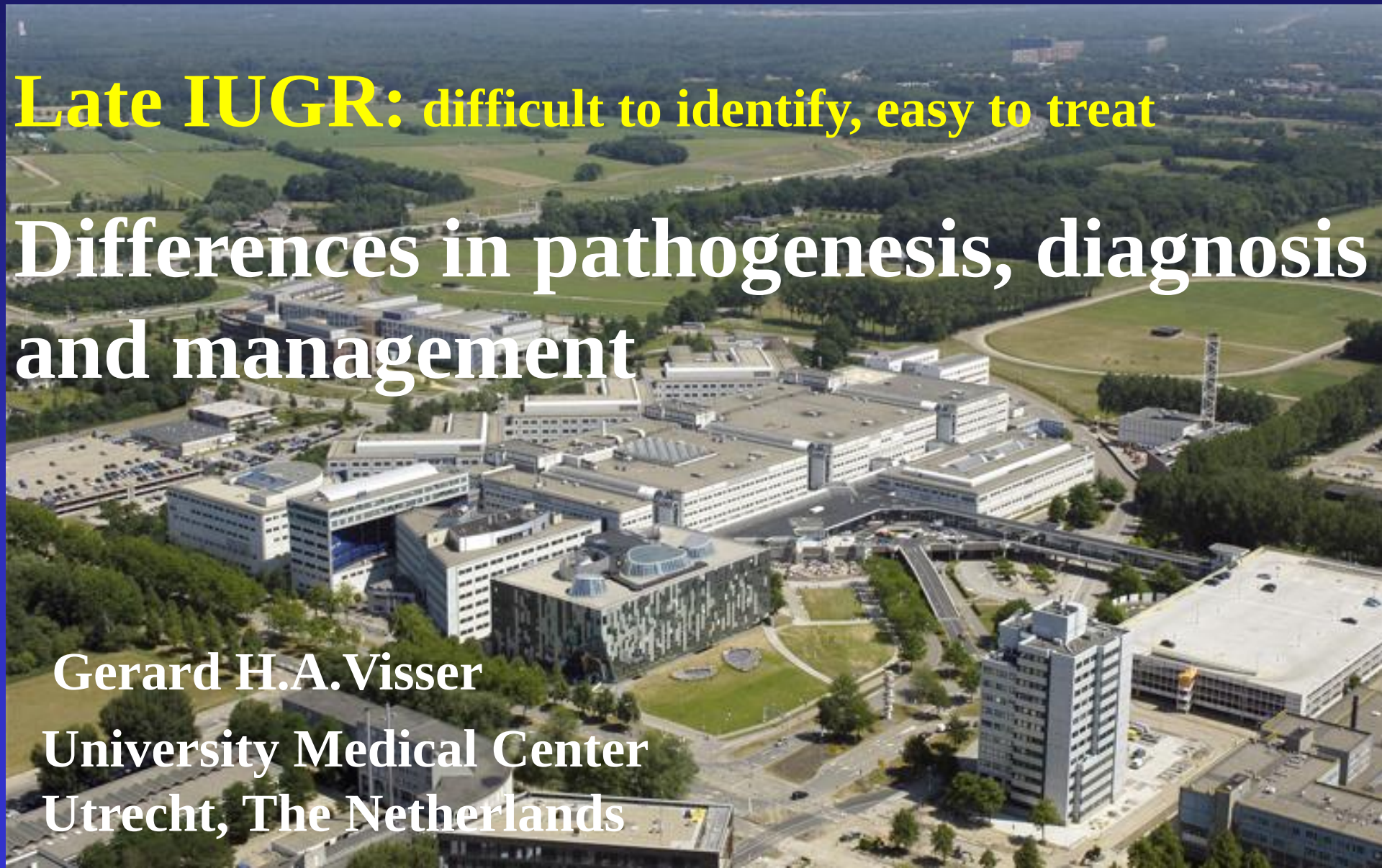
Early IUGR: easy to identify, difficult to treat

Late IUGR: difficult to identify, easy to treat

Differences in pathogenesis, diagnosis and management



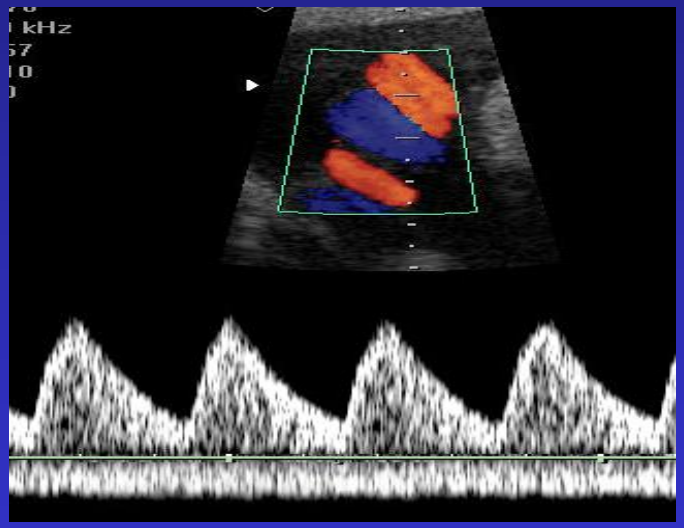
Gerard H.A.Visser

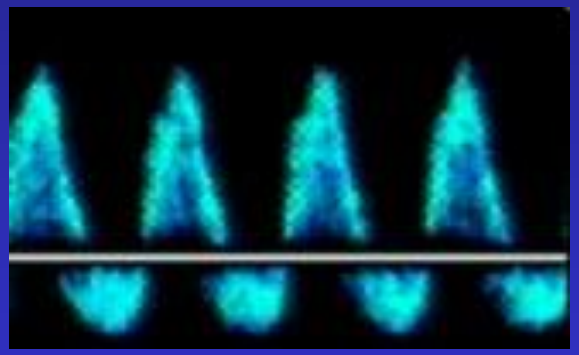
University Medical Center
Utrecht, The Netherlands

Early IUGR: easy to identify

All screening and diagnostic tests work properly

(especially Doppler umbilical artery)





Moreover, 75% of IUGR accompanied by maternal hypertensive disease

So, ……

- Easy identification
- Sufficient monitoring tools

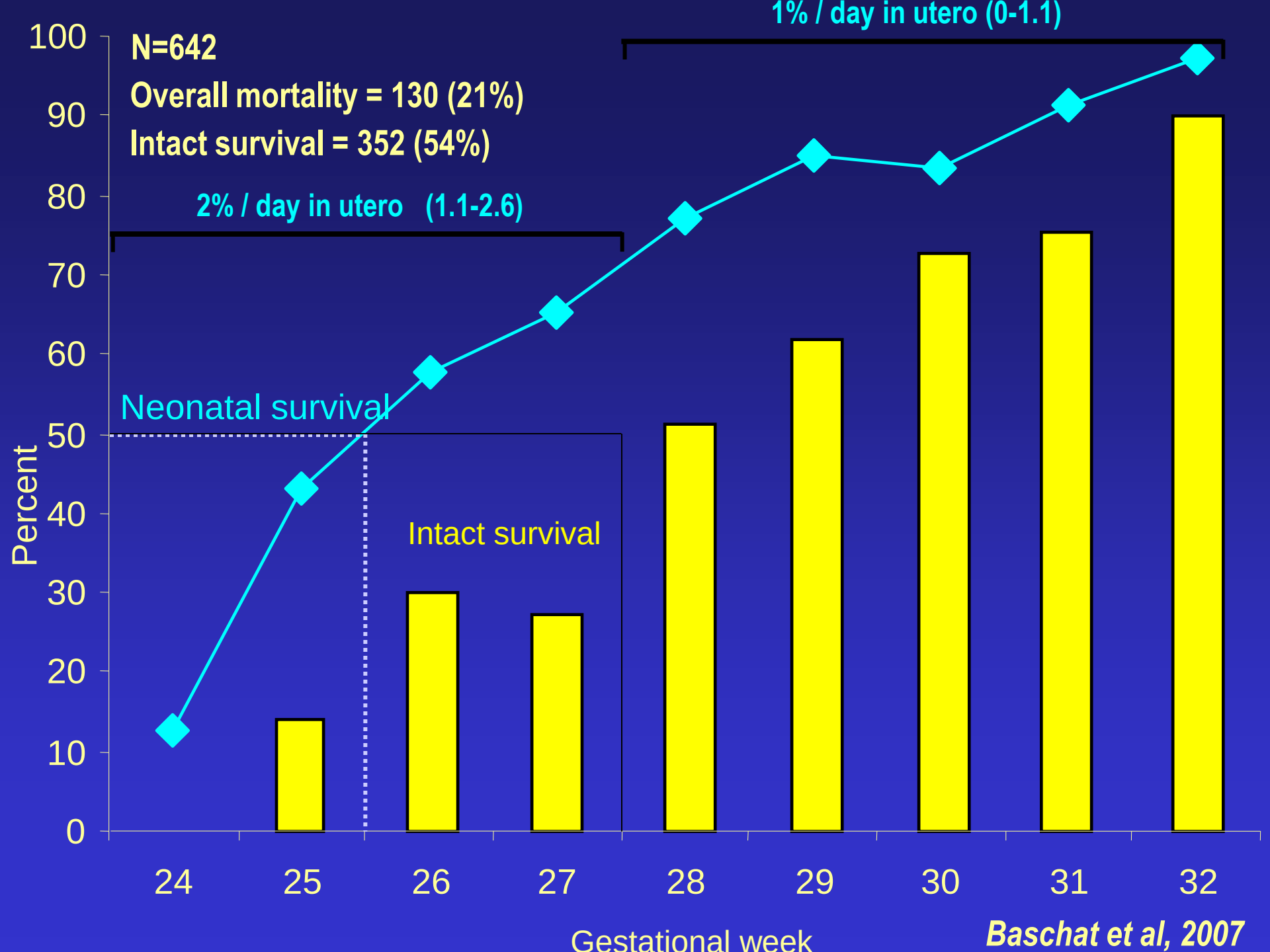
- But,….. what next??
- Therapy: Oxygen?
  Corticosteroids?
  Neuroprevention ($MgSO_4$, Allopurinol)

So, ……

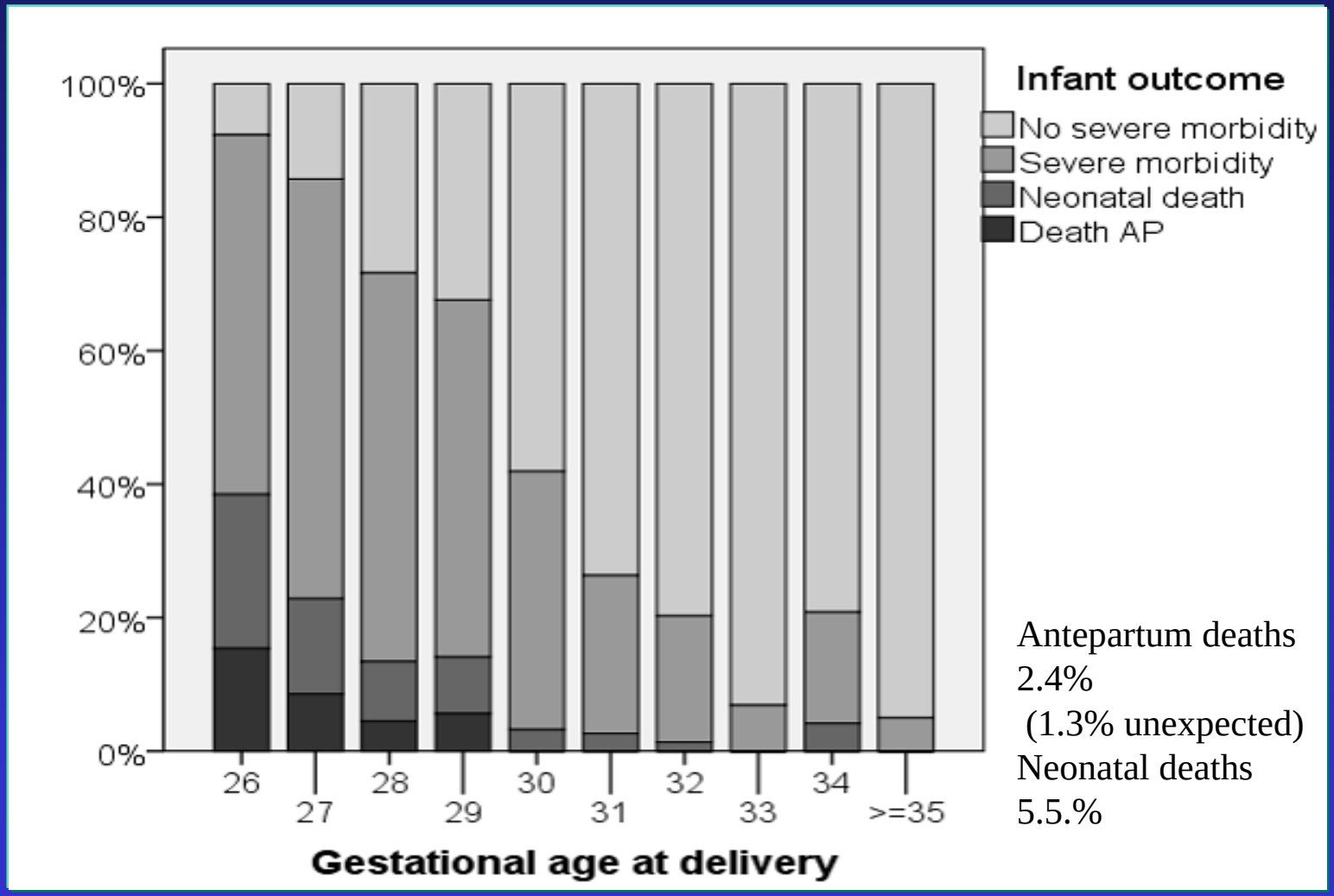
- Easy identification
- Sufficient monitoring tools

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

Thornton et al Lancet 2004, Walker et al AJOG 2011


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

TRUFFLE, Perinatal death & Morbidity



Antepartum deaths
2.4%
(1.3% unexpected)
Neonatal deaths
5.5.%

Lees et al, U O&G Oct 2013

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

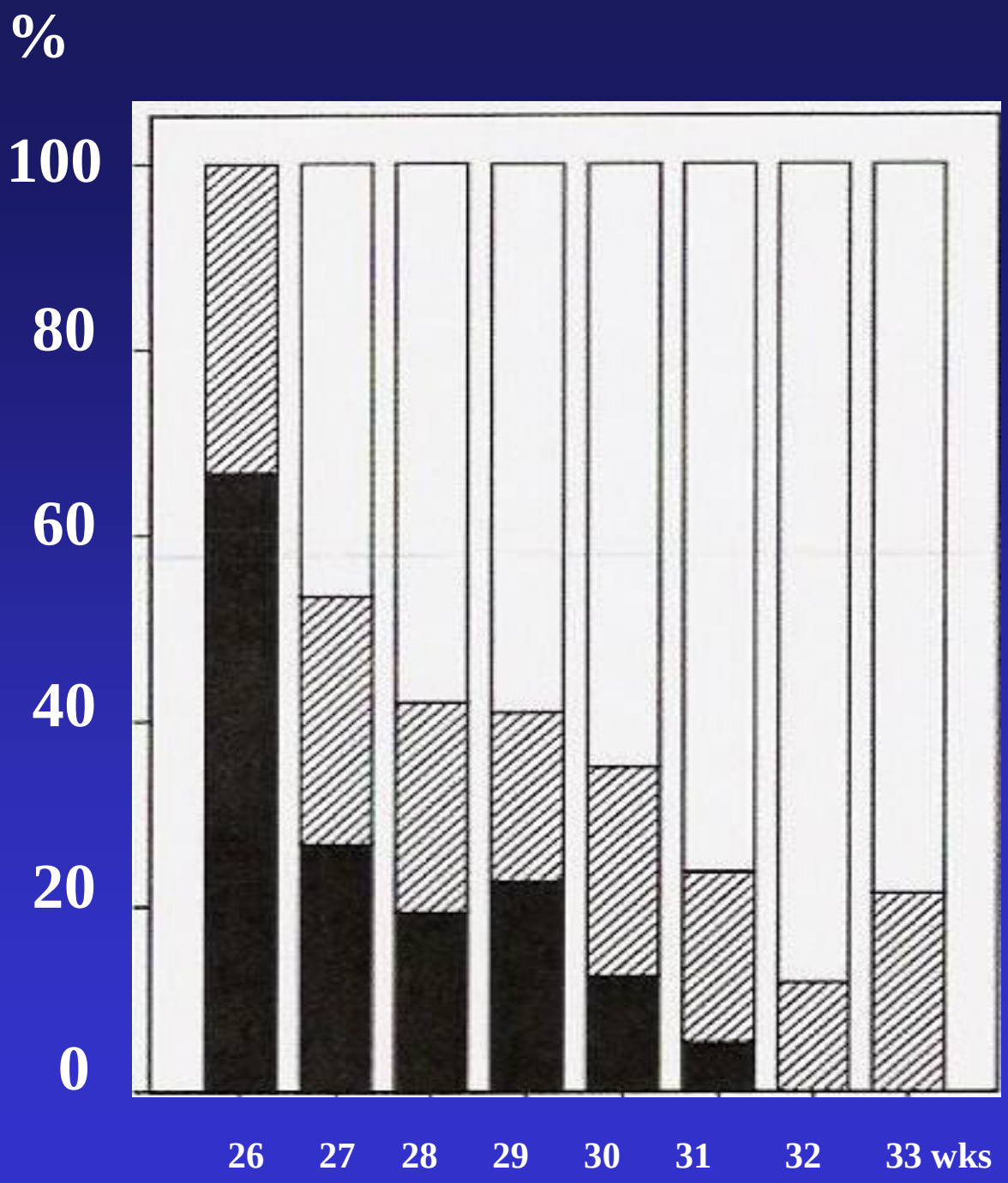
Infant mortality

Neonatal morbidity

Neur.morbidity at 2 years

Torrance et al, UOG, 2010

2 y outcome

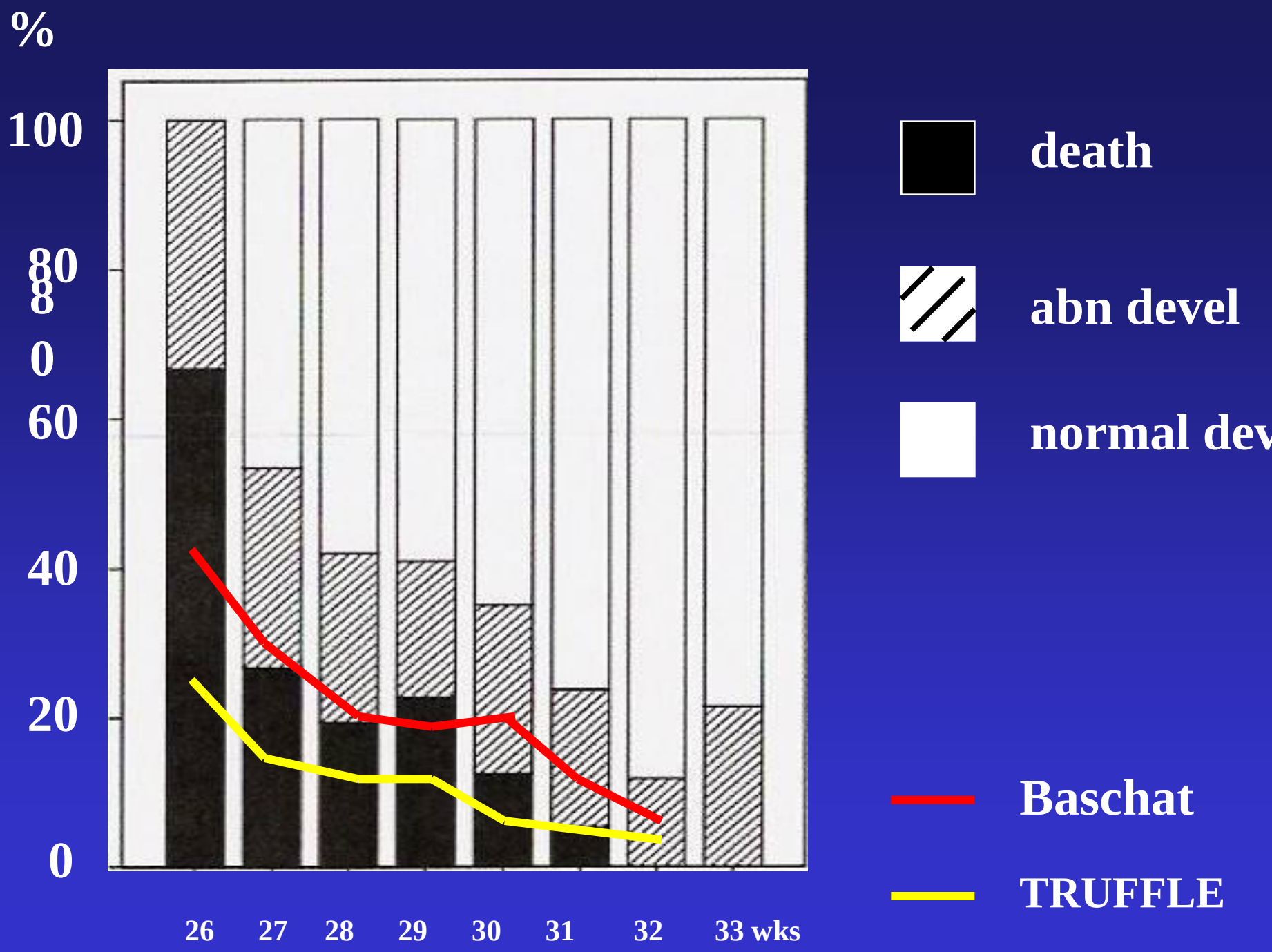


death

abn devel

normal dev

Intact survival at 2 years:
66%
1 case of CP only
Torrance et al,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

Morphological findings in human IUGR infants and in animal models

- Smaller brain size (grey matter volume), fewer cells, reduced total DNA in glial cell and neurons, deficits in synapse-to-neurone ratios, reduced dendritic growth
- Rather than localized lesions (which occur after (acute) asphyxia)

Chase et al, 1972; Dobbing,1974; Bedi, 1984; Kreusser & Volpe, 1984; Toft et al, 1995

Morphological findings in human IUGR infants and in animal models

- Smaller brain size (grey matter volume), fewer cells, reduced total DNA in glial cell and neurons, deficits in synapse-to-neurone ratios, reduced dendritic growth
- Rather than localized lesions (which occur after (acute) asphyxia)

Redistribution, increased oxygen extraction, increased transport (Hb)

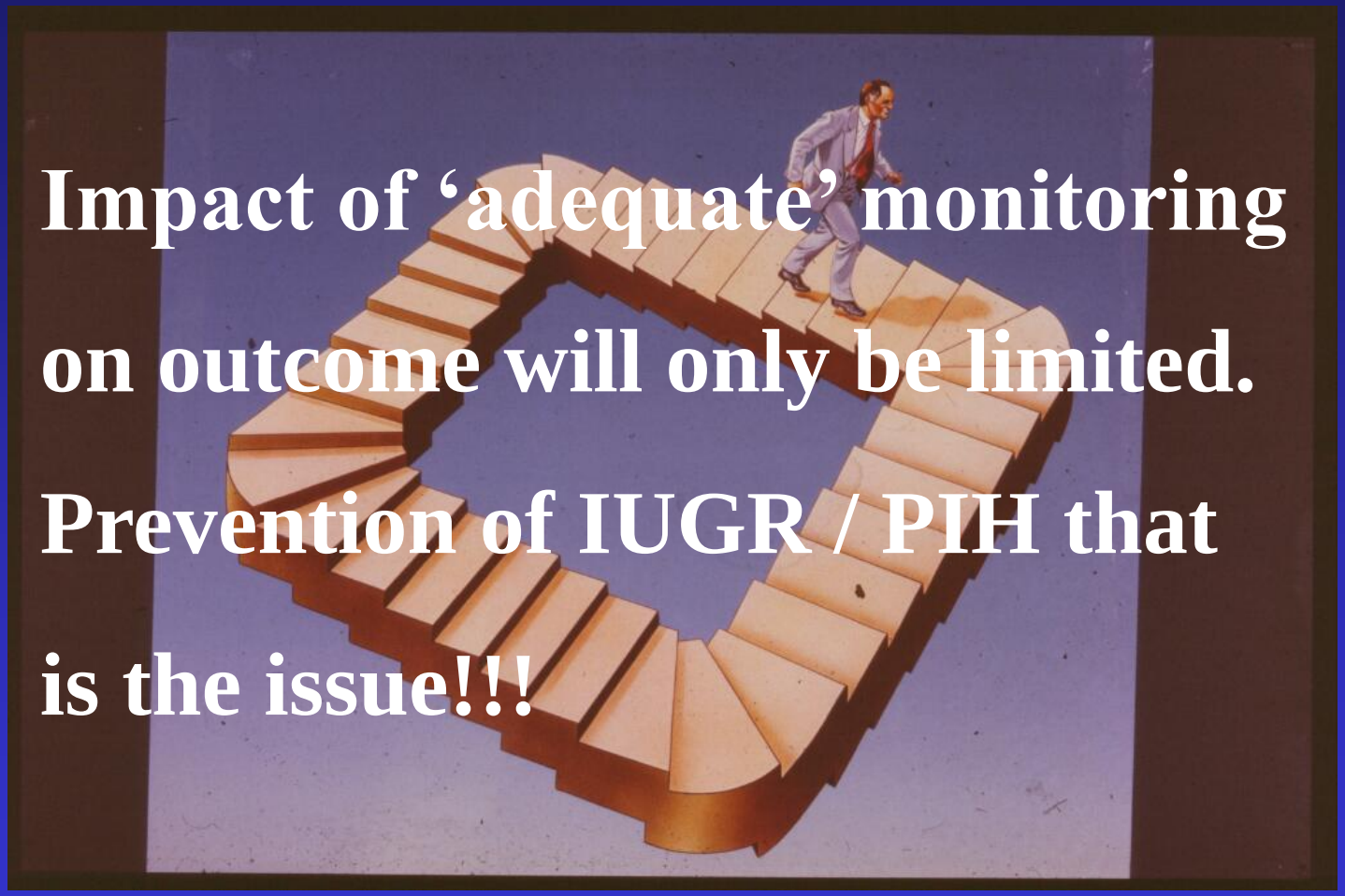
Chase et al, 1972; Dobbing,1974; Bedi, 1984; Kreusser & Volpe, 1984; Toft et al, 1995

In the early IUGR fetus

- brain damage is likely to be caused by malnutrition, rather than by hypoxaemia

- Which hampers adequate treatment options

All in all,



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

University Medical Center, Utrecht, the NL

-Early identification: 12 wks: Doppler, RR, plac proteins

- Primary prevention (aspirin, Viagra, L-arginine, Ca)

~~Timing of delivery~~

Gerard H.A.Visser

Prevention of PE with aspirin

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

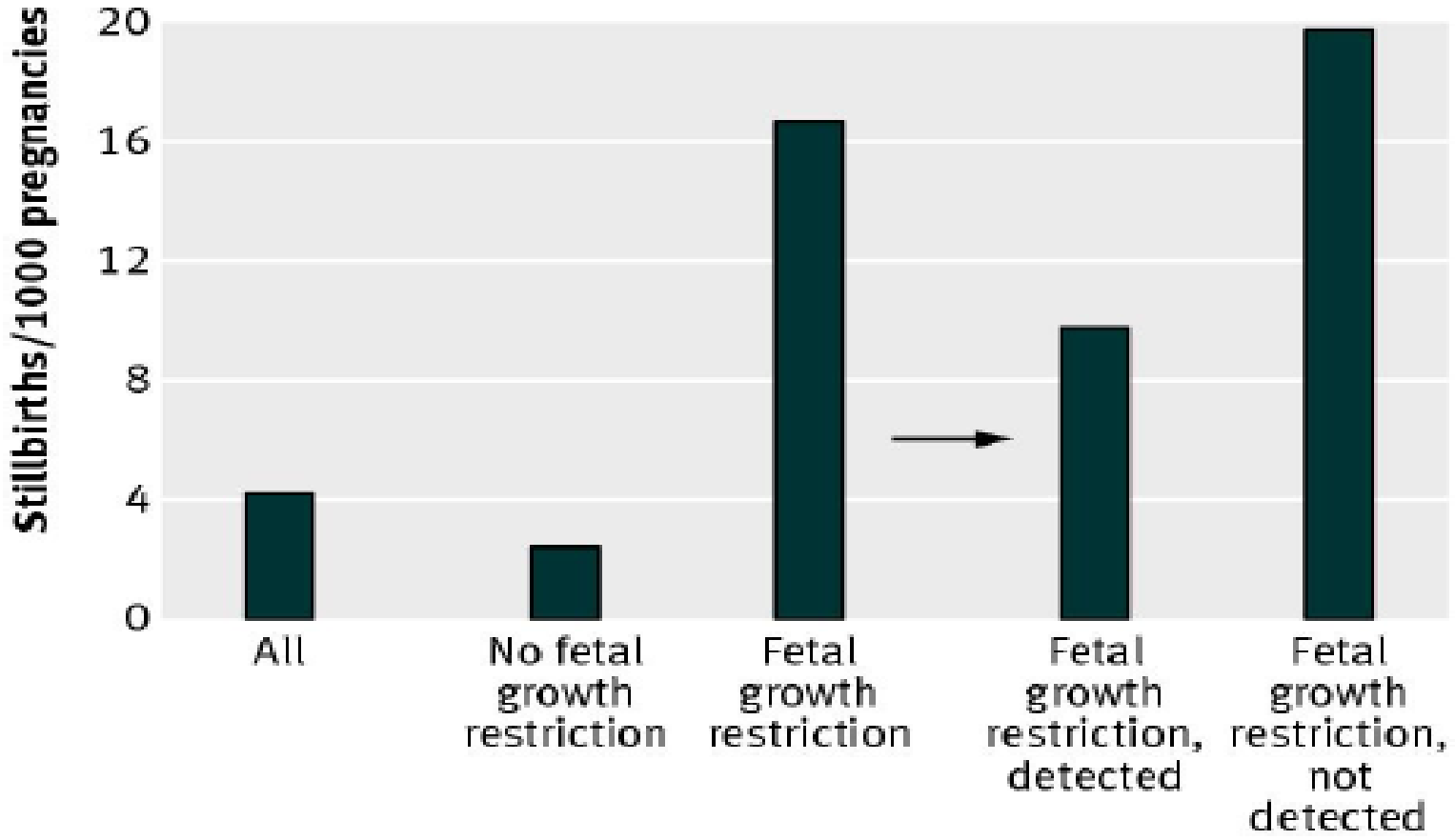
- Metanalysis 27 RCTs 11.348 patients, early-late start of Aspirin (Bujold et al 2010):
- =< 16 wks RR 0.47 (CI 0.34-0.65) IUGR RR 0.44 (CI 0.30-0.65)

- > 16 wks RR 0.81 ns IUGR RR 0.98 ns

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

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

Stillbirth rate in relation to FGR



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

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)

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

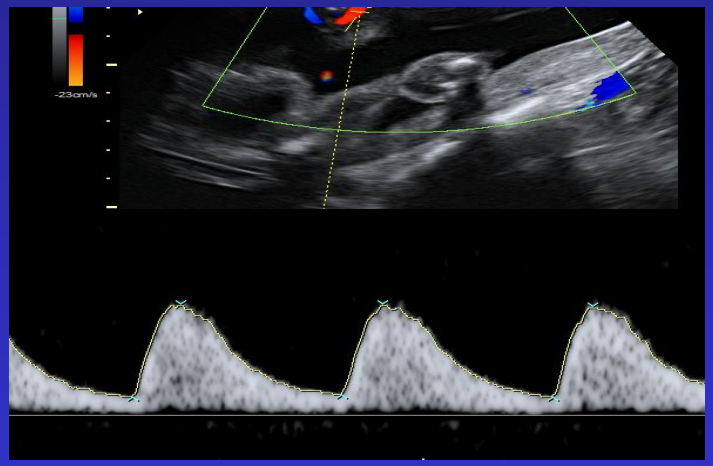
Term IUGR/SGA

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

Term IUGR/SFD

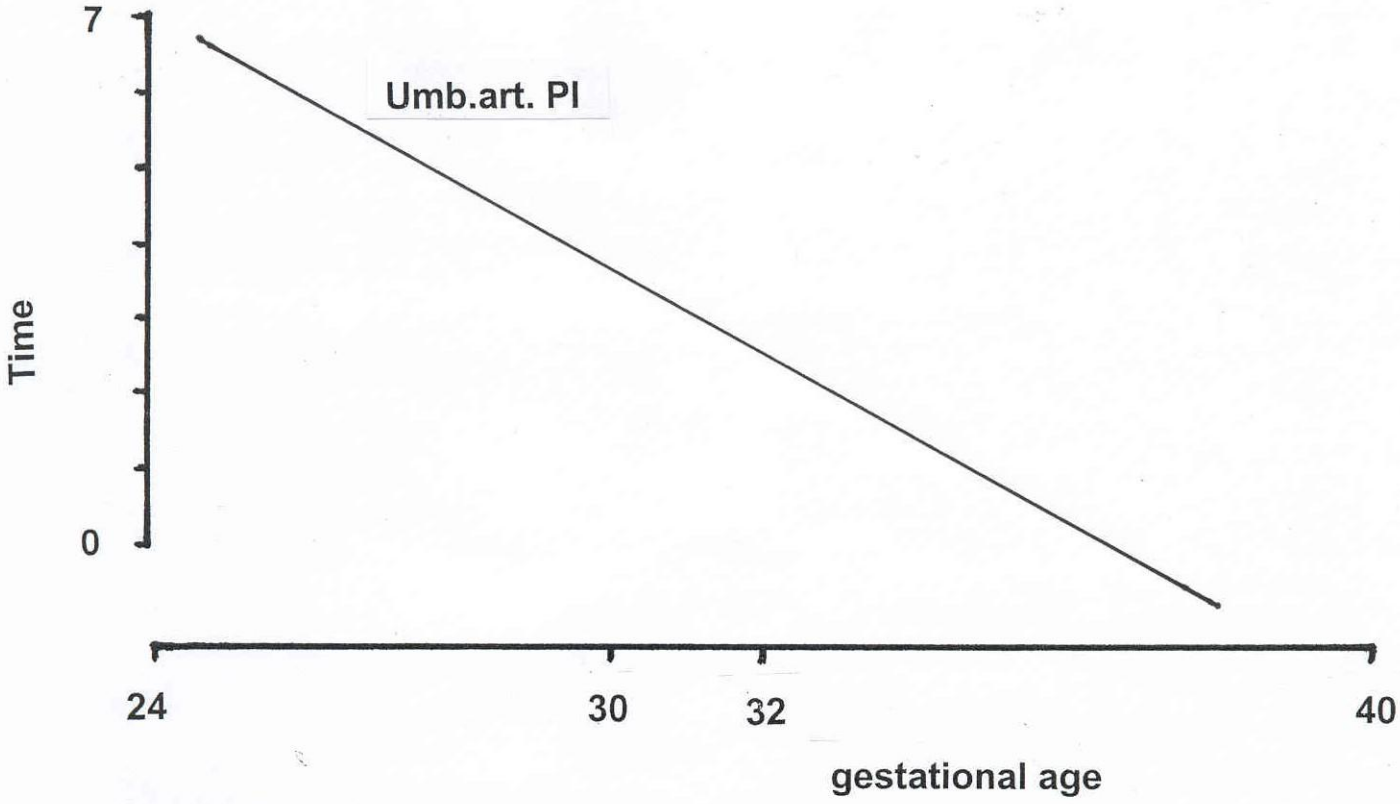
Many screening and diagnostic tests do not work properly

(and that holds especially for Doppler umbilical artery)



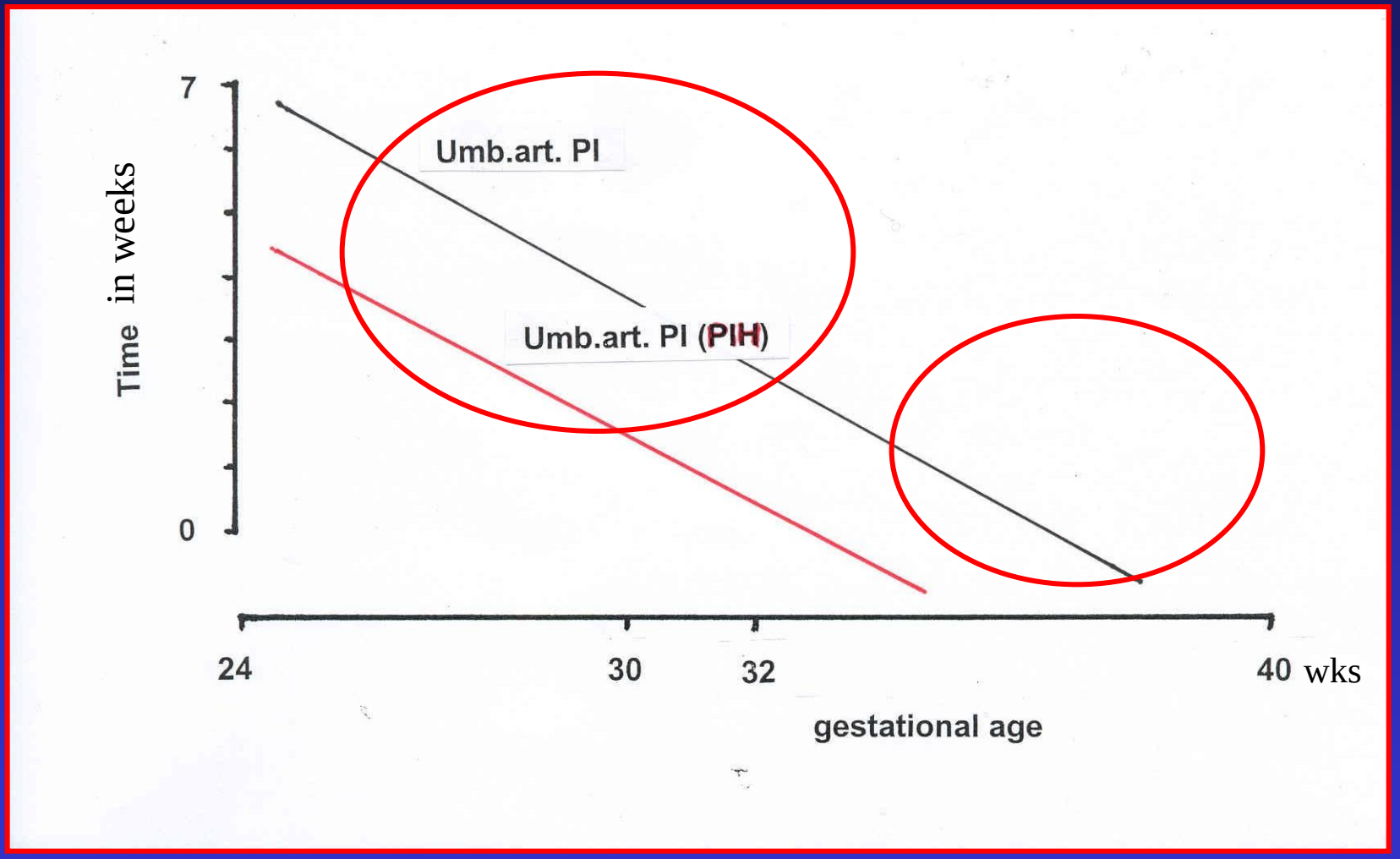
Moreover, IUGR is not accompanied by maternal hypertensive disease

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

- **Assessment techniques:**

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

Structured information on fetal movements at 18 wks

- 65 % reduction in IUFD in nulliparous women (OR 0.36, 95%CI 0.19-0.69)
- No change in multparous women, smokers, obese women, maternal age >34 y, foreigners

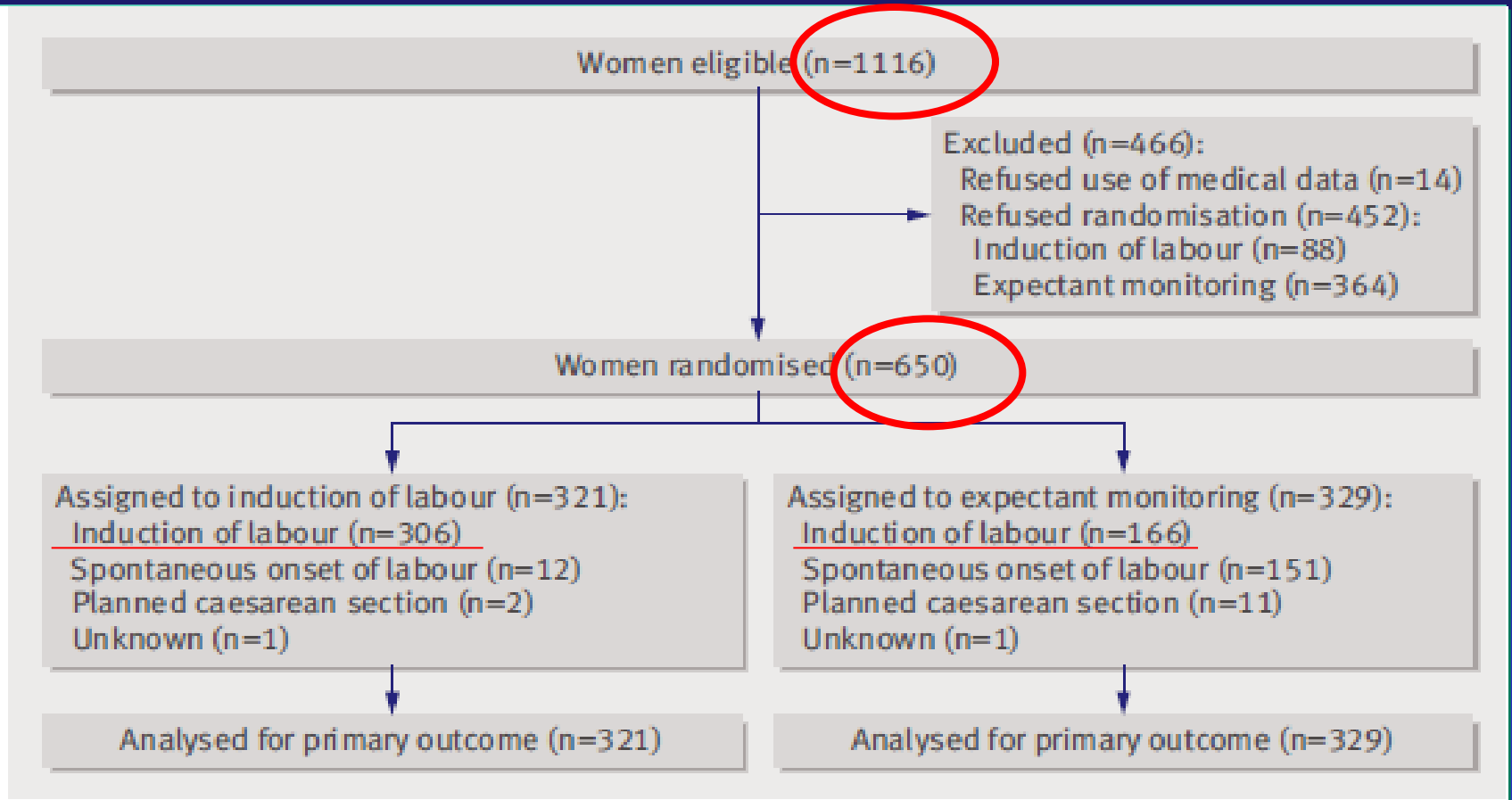
Saastad e.s. BMC Research notes, 2010,3:2

Identification of the late IUGR fetus

- 1- First trimester risk screening
- 2- 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; when?

DIGITAT study



Flow diagram of the trial process

BMJ | ONLINE FIRST | bmj.com **Broers et al, 2010**

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

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

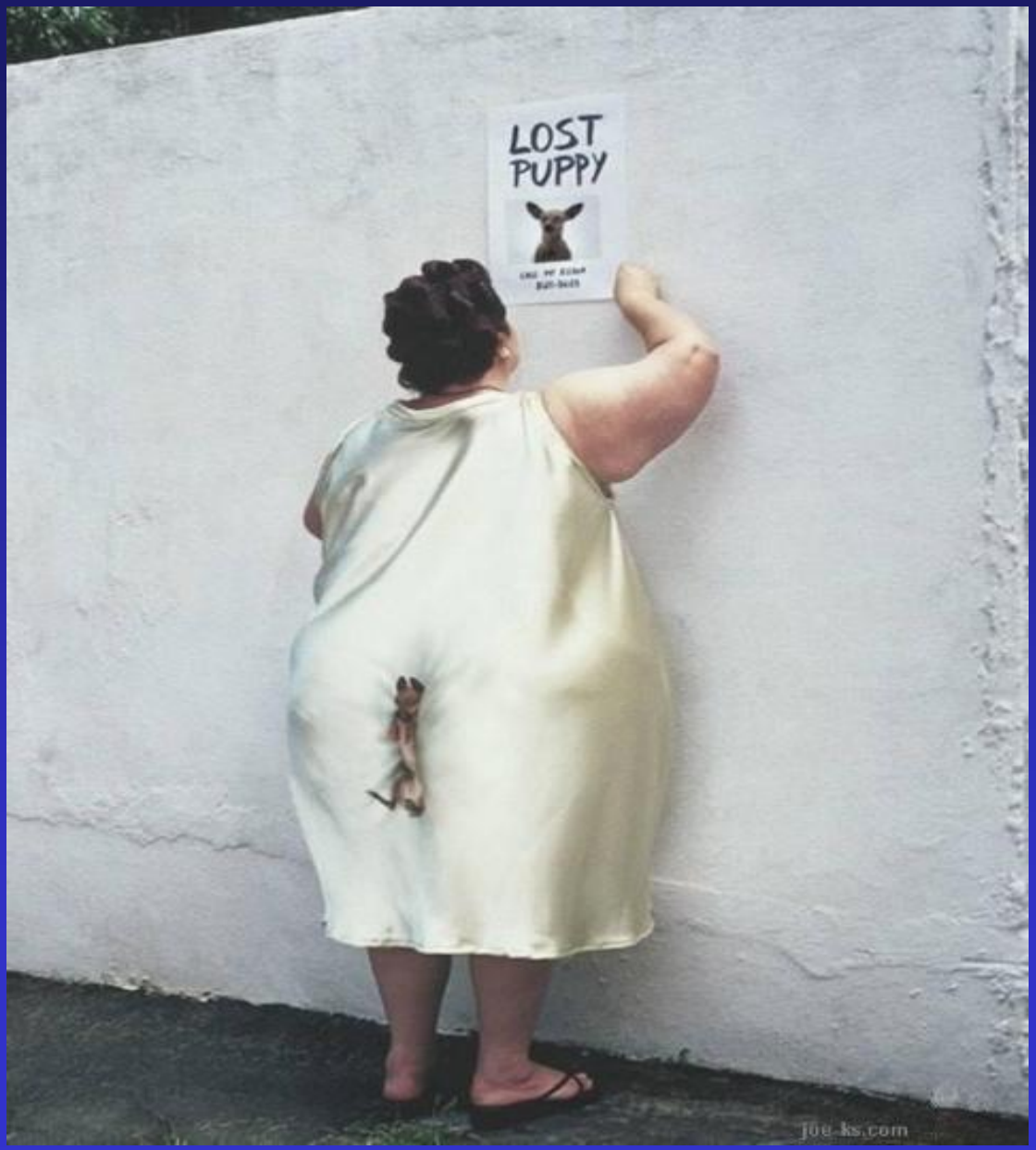
Van Wijk et al, AJOG 2012, May, 206(5) 406,e1-7

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

Individualize, start thinking

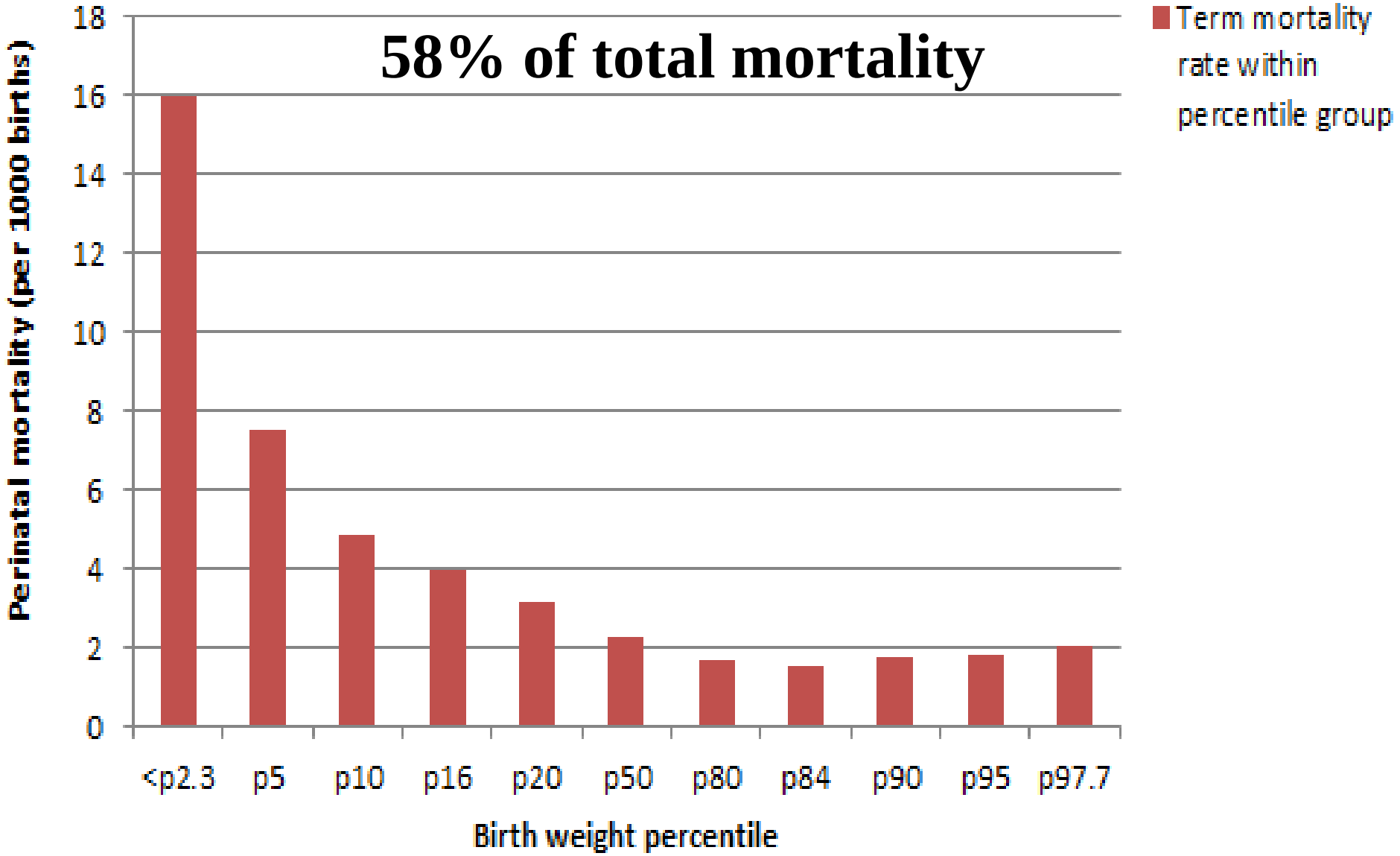

LOST
PUPPY
joe-ks.com

Perinatal mortality and birth weight centiles

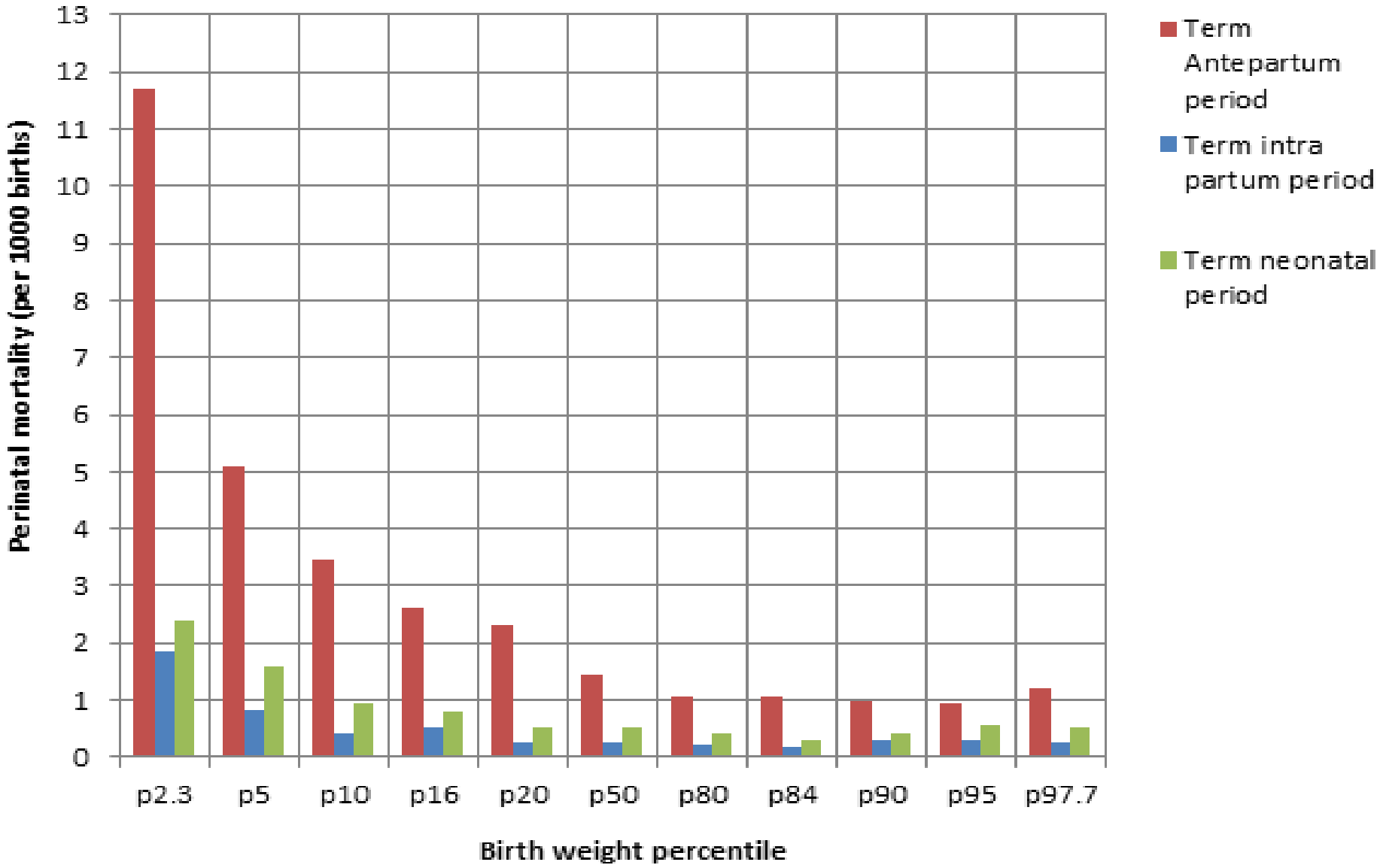
- 70 percent of perinatal mortality in infants without congenital malformations occurs in infants > 10^{th} centile

Vasak et al, 2014

Perinatal mortality >+36 wks, Nlds 2000-2008



Perinatal mortality >= 36 wks



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

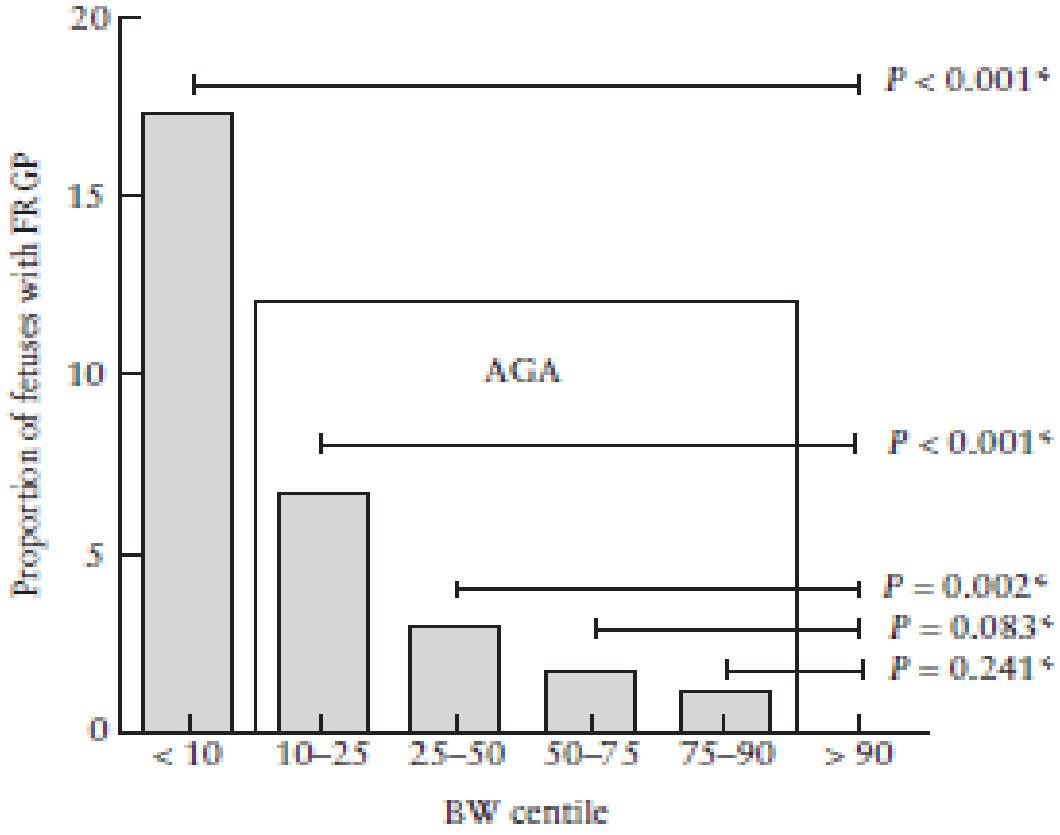


Figure 3 Percentage of term fetuses with failure to reach growth potential (FRGP) according to their birth weight (BW) centile group (i.e. percentage of fetuses presenting a cerebroplacental ratio (CPR) multiple of the median (MoM) value below the established FRGP normality threshold (CPR MoM = 0.6765), 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

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

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 ’

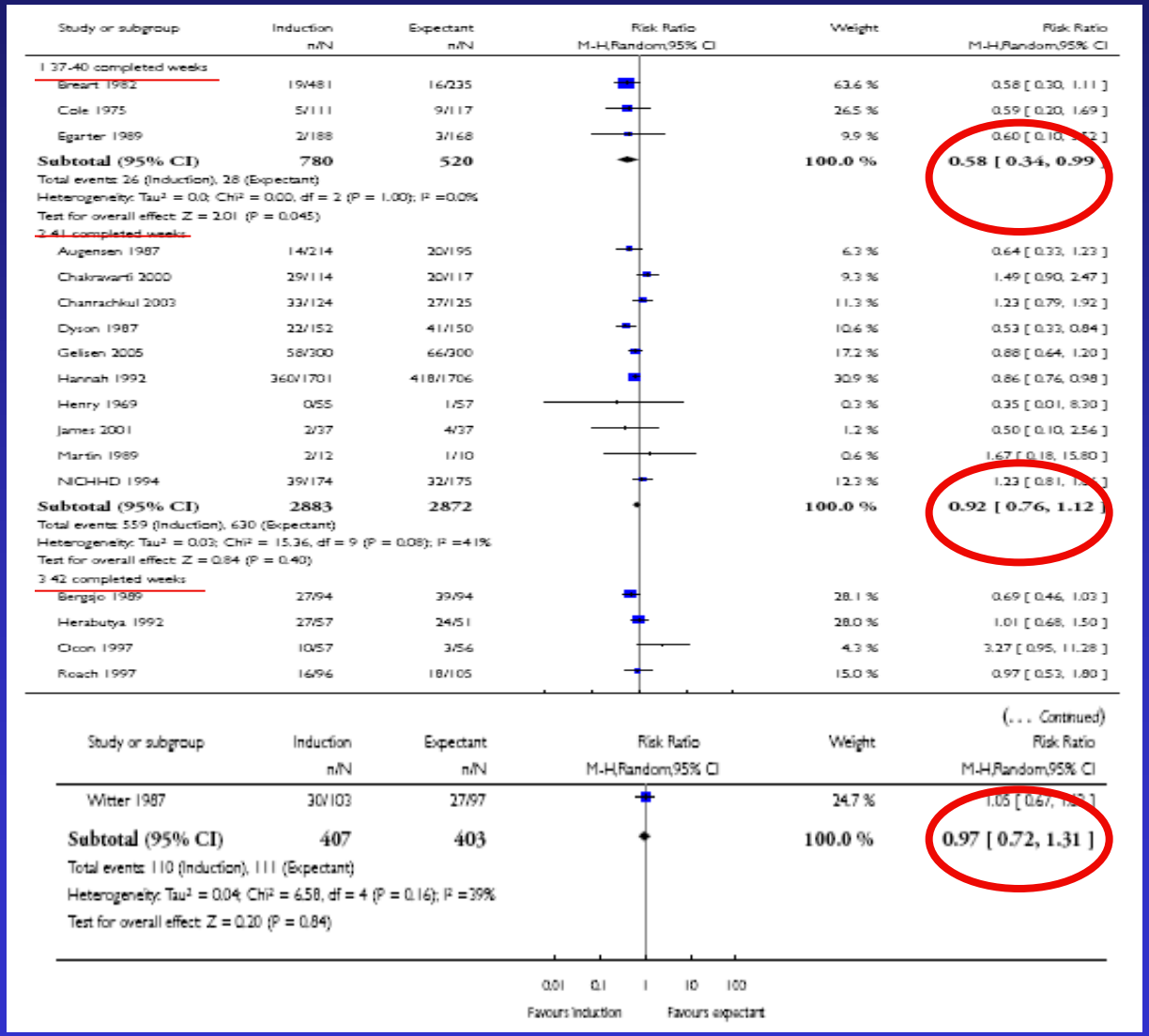
And,……..

Cochrane: induction vs expectant management

37-40 wks

>41 wks

> 42 wks



Study or subgroup	Induction n/N	Expectant n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 37-40 completed weeks					
Breart 1982	19/481	16/235		63.6 %	0.58 [0.30, 1.11]
Cole 1975	5/111	9/117		26.5 %	0.59 [0.20, 1.69]
Egarter 1989	2/188	3/168		9.9 %	0.60 [0.10, 3.52]
Subtotal (95% CI)	**780**	**520**		**100.0 %**	**0.58 [0.34, 0.99]**
Total events: 26 (Induction), 28 (Expectant)					
Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 2 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 2.01 (P = 0.045)					
2 41 completed weeks					
Augensen 1987	14/214	20/195		6.3 %	0.64 [0.33, 1.23]
Chakravarti 2000	29/114	20/117		9.3 %	1.49 [0.90, 2.47]
Chanrachkul 2003	33/124	27/125		11.3 %	1.23 [0.79, 1.92]
Dyson 1987	22/152	41/150		10.6 %	0.53 [0.33, 0.84]
Gelisen 2005	58/300	66/300		17.2 %	0.88 [0.64, 1.20]
Hannah 1992	360/1701	418/1706		30.9 %	0.86 [0.76, 0.98]
Henry 1969	0/55	1/57		0.3 %	0.35 [0.01, 8.30]
James 2001	2/37	4/37		1.2 %	0.50 [0.10, 2.56]
Martin 1989	2/12	1/10		0.6 %	1.67 [0.18, 15.80]
NICHHD 1994	39/174	32/175		12.3 %	1.23 [0.81, 1.86]
Subtotal (95% CI)	**2883**	**2872**		**100.0 %**	**0.92 [0.76, 1.12]**
Total events: 559 (Induction), 630 (Expectant)					
Heterogeneity: Tau² = 0.03; Chi² = 15.36, df = 9 (P = 0.08); I² =41%					
Test for overall effect: Z = 0.84 (P = 0.40)					
3 42 completed weeks					
Bergsjo 1989	27/94	39/94		28.1 %	0.69 [0.46, 1.03]
Herabutya 1992	27/57	24/51		28.0 %	1.01 [0.68, 1.50]
Olson 1997	10/57	3/56		4.3 %	3.27 [0.95, 11.28]
Roach 1997	16/96	18/105		15.0 %	0.97 [0.53, 1.80]

(. . . Continued)

Study or subgroup	Induction n/N	Expectant n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Witter 1987	30/103	27/97		24.7 %	1.05 [0.67, 1.63]
Subtotal (95% CI)	**407**	**403**		**100.0 %**	**0.97 [0.72, 1.31]**
Total events: 110 (Induction), 111 (Expectant)					
Heterogeneity: Tau² = 0.04; Chi² = 6.58, df = 4 (P = 0.16); I² =39%					
Test for overall effect: Z = 0.20 (P = 0.84)					

0.01 0.1 1 10 100

Favours induction Favours expectant

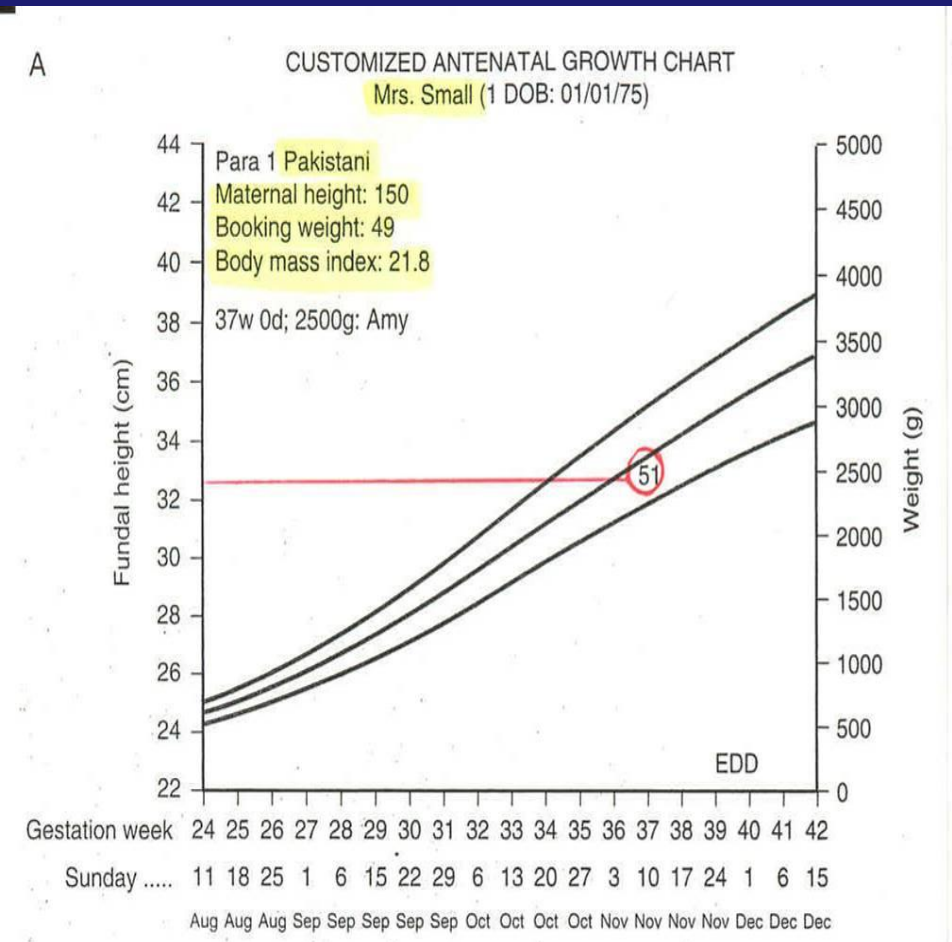
“ I am a fetus in the womb
I fear it may become my tomb
if only I could give a shout
to get my doctor to get me
out!”

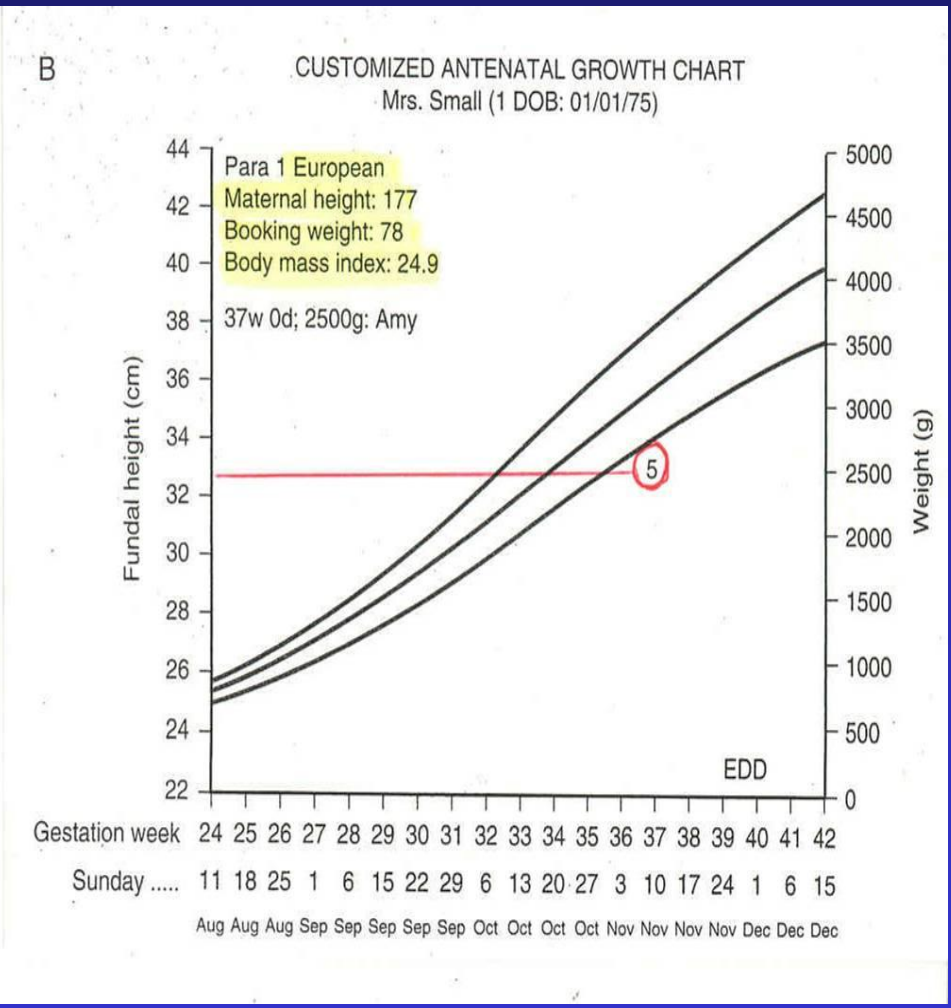
a British Medical Student

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

Customized antenatal growth chart





(Gardosi et al, 2005)

Late onset IUGR; uterine artery

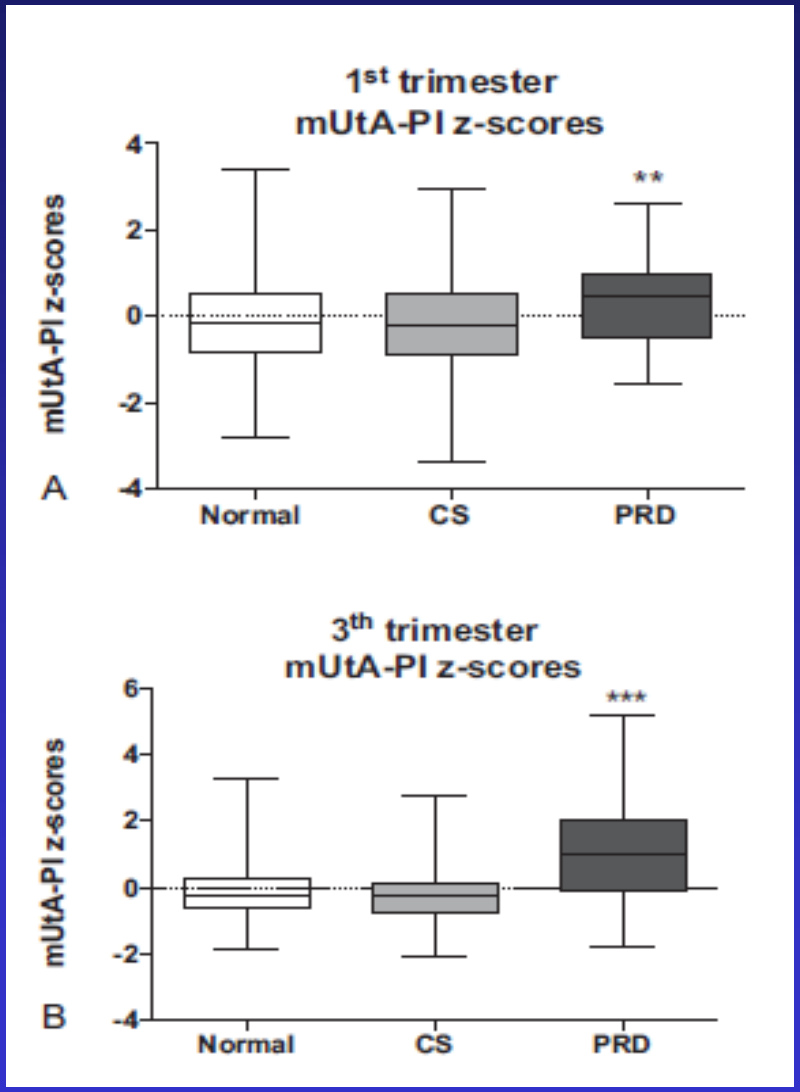
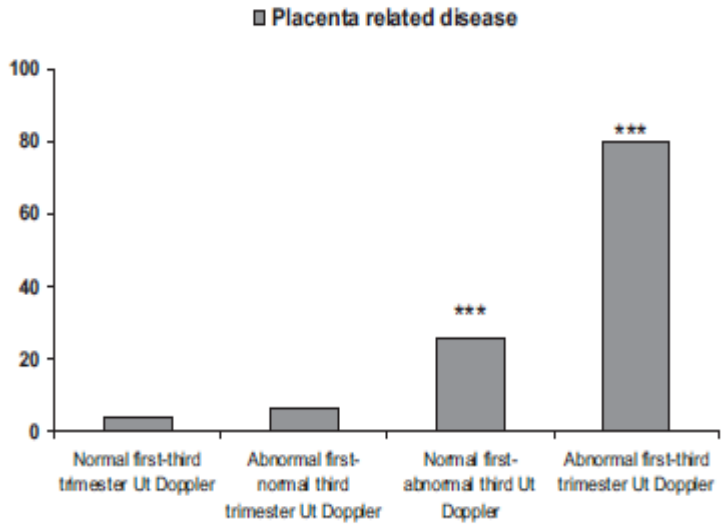


Table 4 Concordance between first- and third-trimester abnormal mUtA-PI z-scores

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

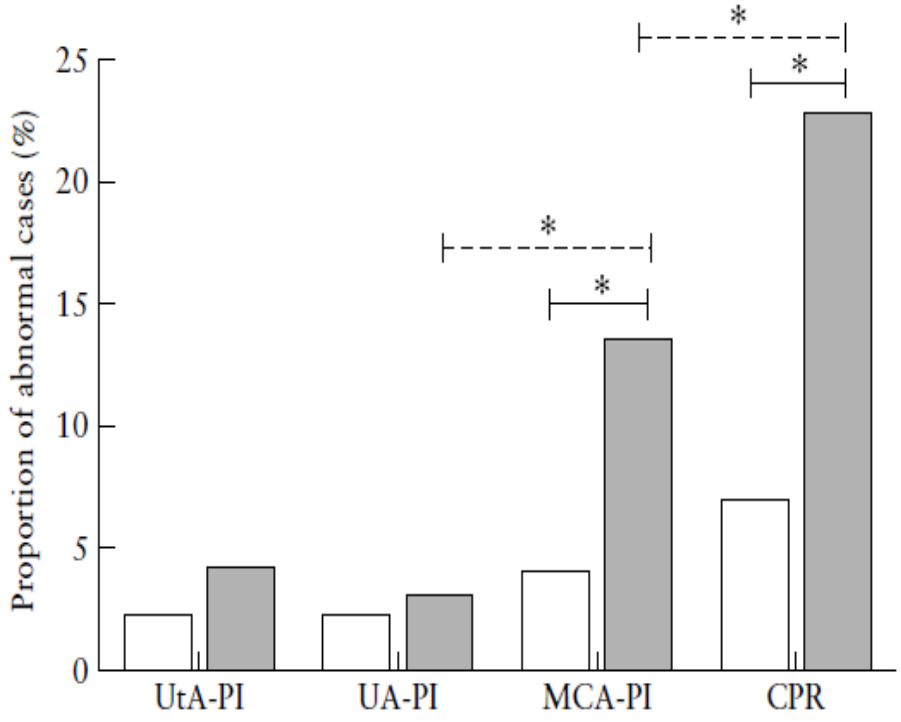
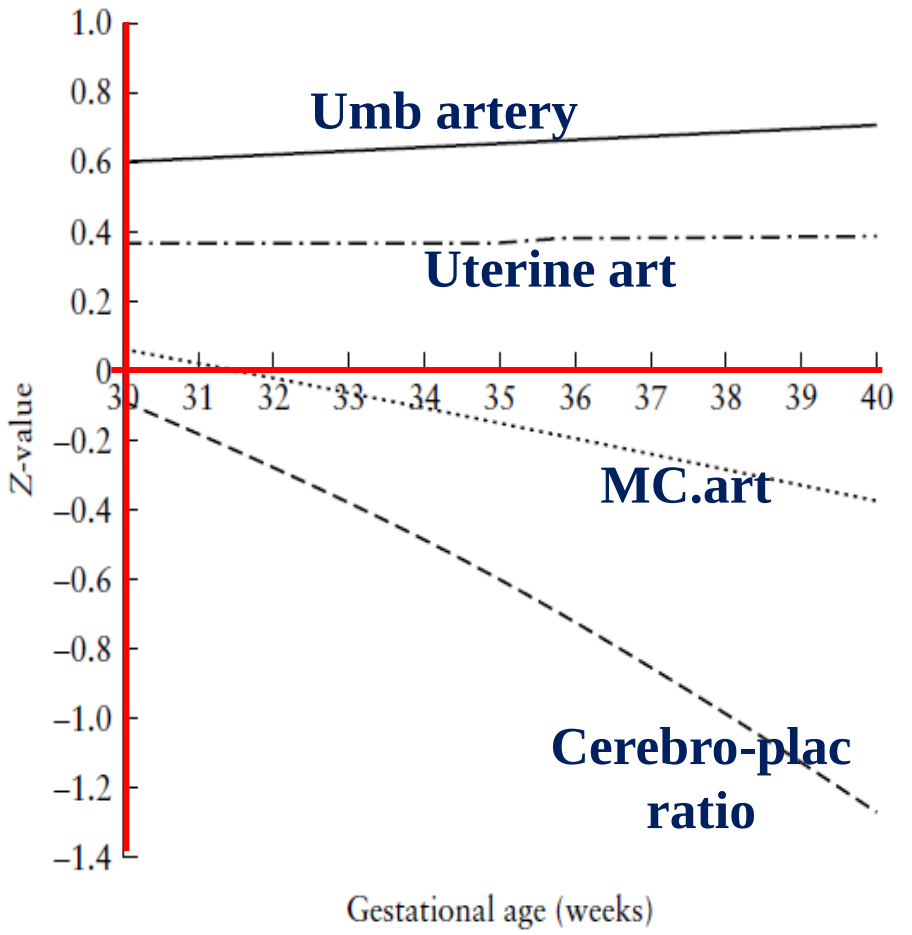


Figure 1 Proportion of abnormal Doppler findings at 37 weeks' gestation (□) and last examination before delivery (▨) (*McNemar $P < 0.05$). CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.



Oros et al, UOG 2010

CS and acidosis according to redistribution or not

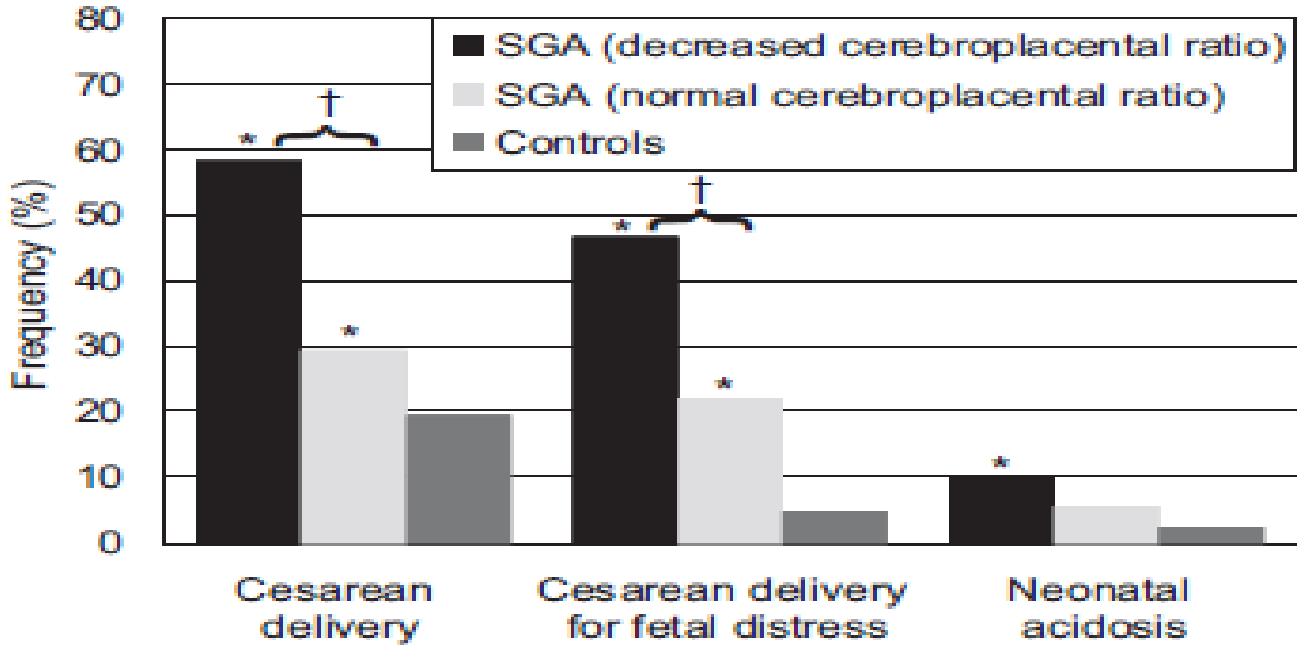
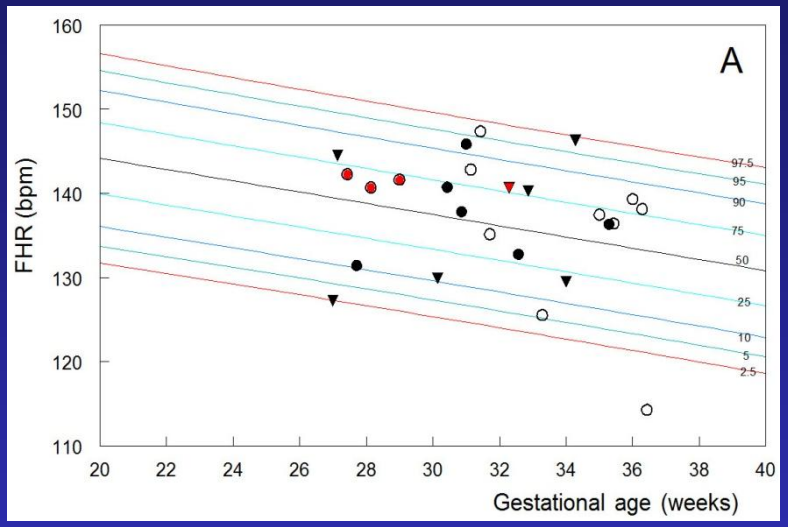
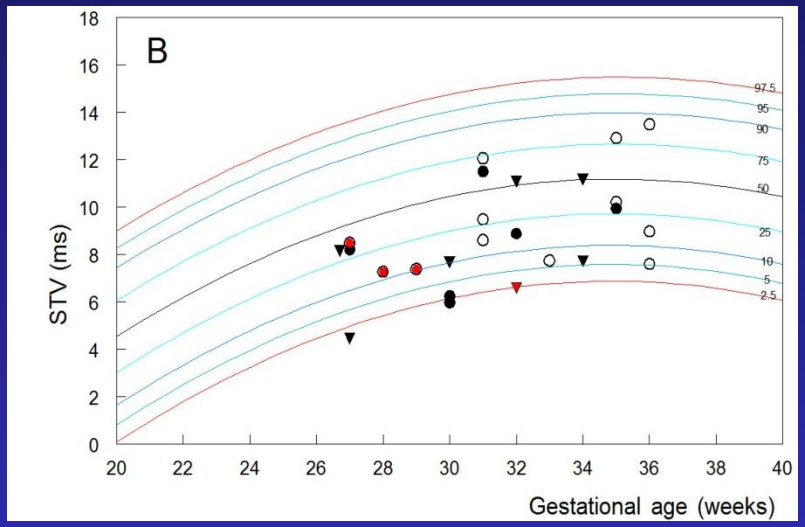


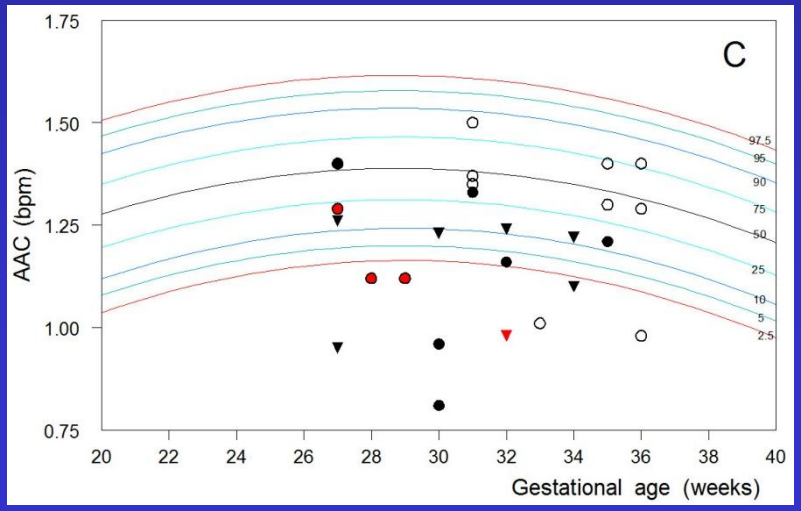
Fig. 2. Frequency of intrapartum cesarean delivery, emergency cesarean for nonreassuring fetal status, and neonatal acidosis in controls and small-for-gestational age (SGA) fetuses with and without decreased cerebroplacental ratio. *$P<.05$ with control participants the reference group; †$P<.01$ among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

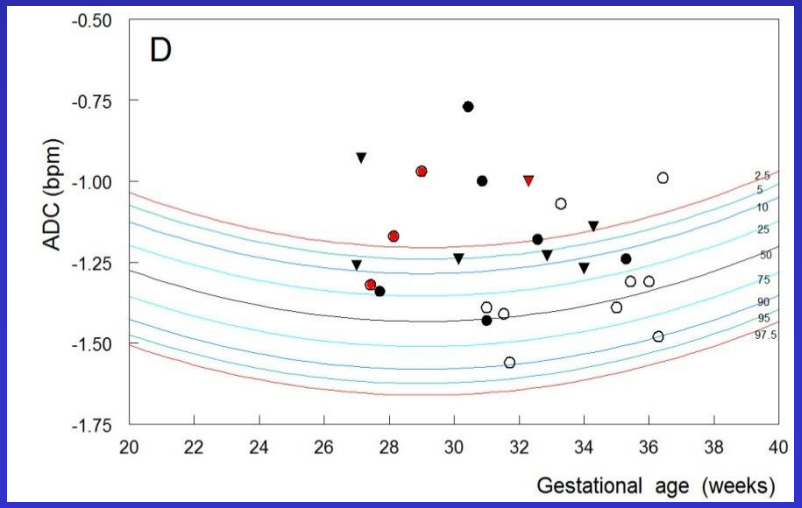
Cruz-Martínez. Brain Doppler and Fetal Status in Small-for-

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









Graatsma et al ,JMFNM 2012

First trimester markers

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

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 all PLOS One, 2013

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 50^{th} 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

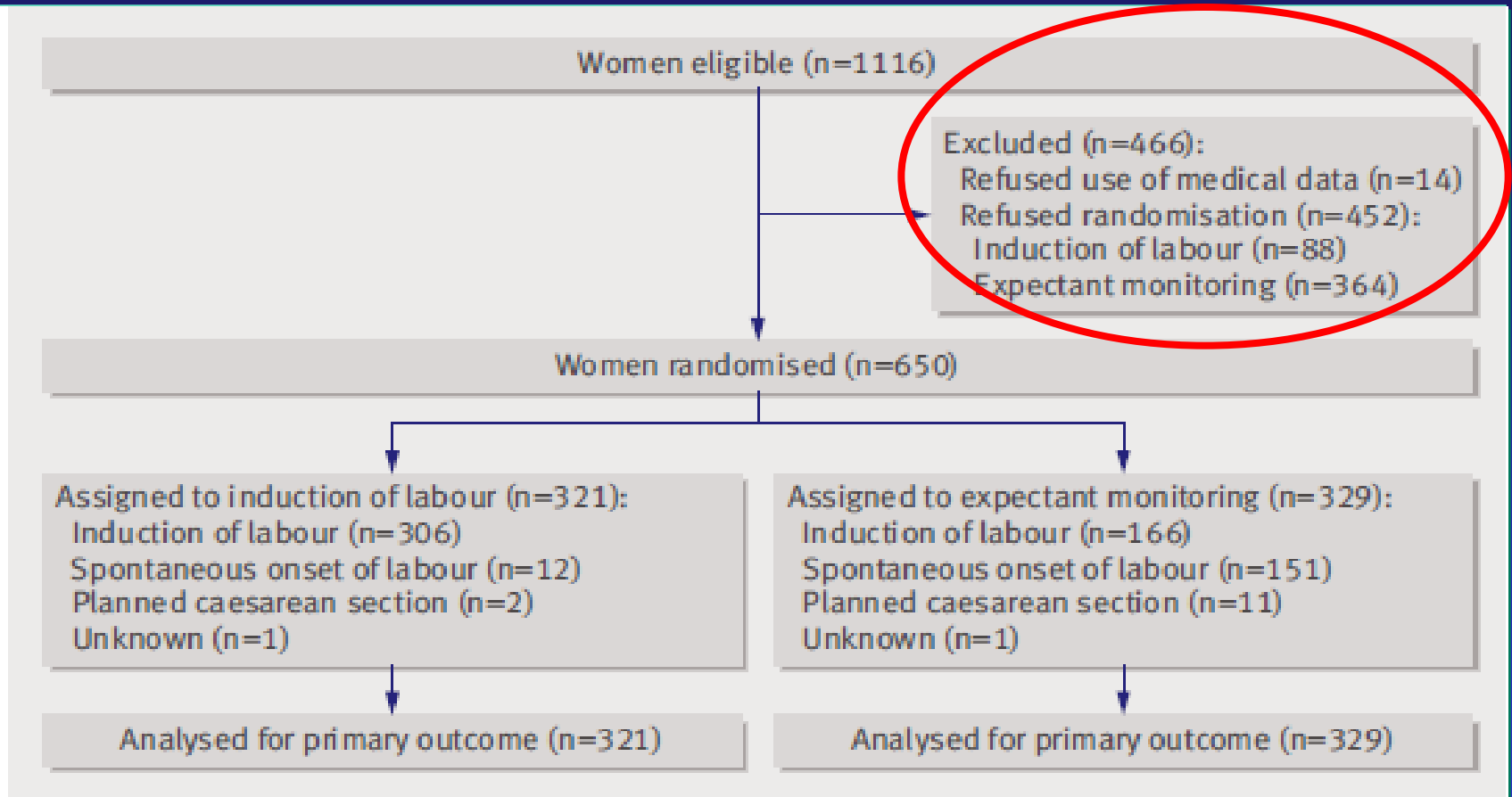
*Digitat study

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

DIGITAT study



Flow diagram of the trial process

BMJ | ONLINE FIRST | bmj.com

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

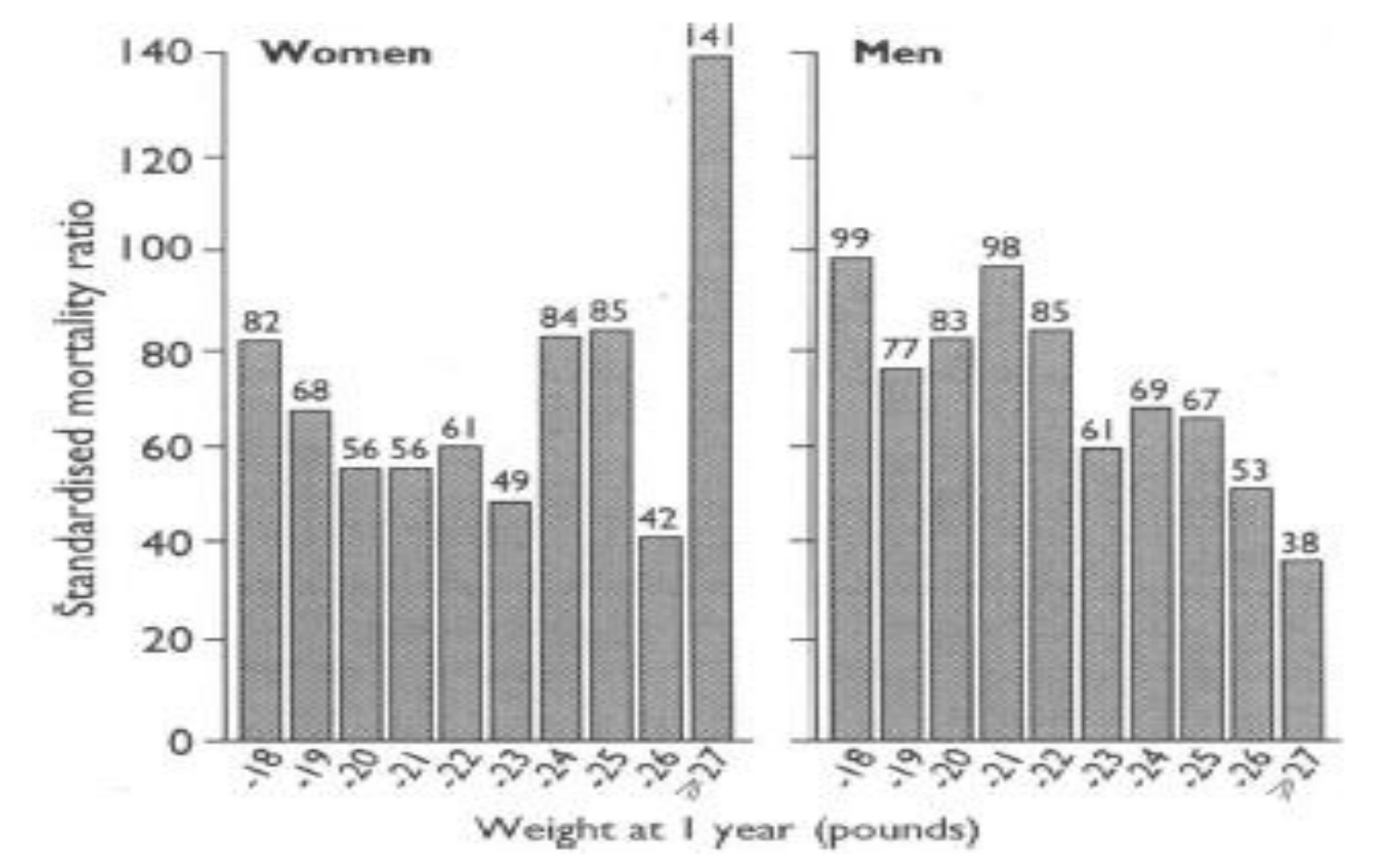


FIG 2—*Standardised mortality ratios for cardiovascular disease below age of 65 according to weight at 1 year*

Osmond et al, BMJ 1993

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

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

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

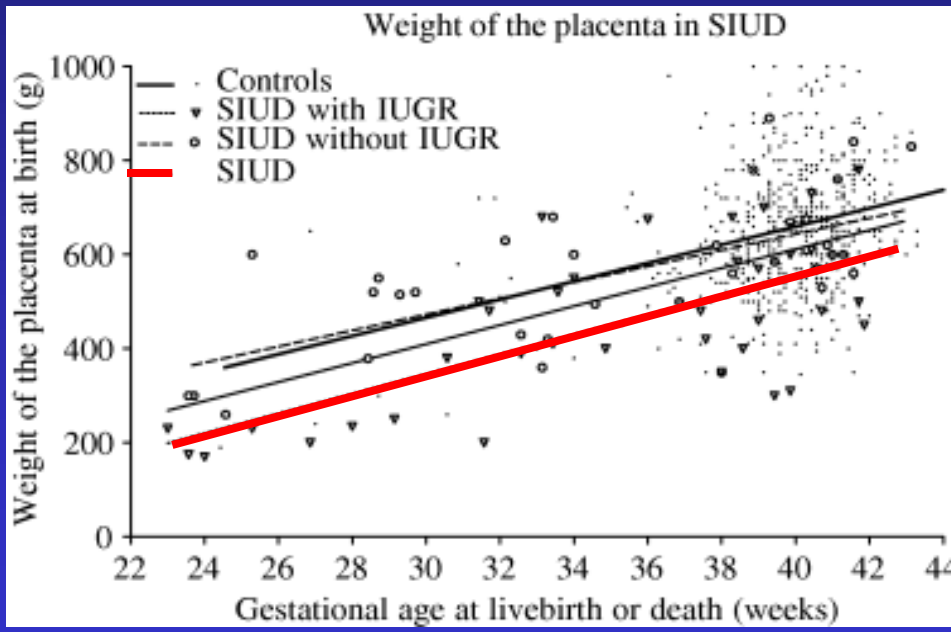

Thank you

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

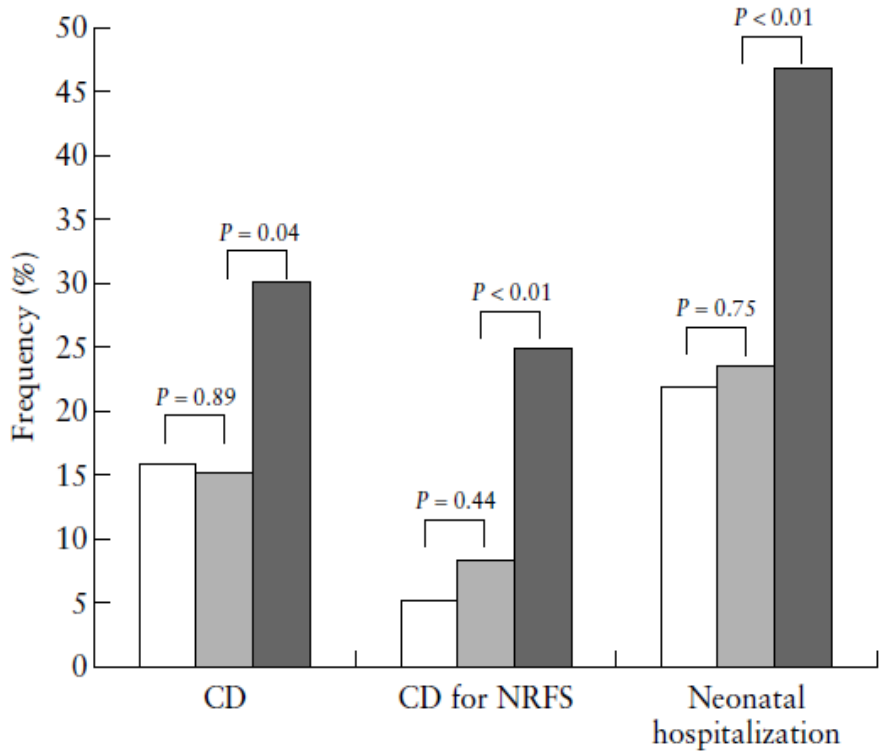


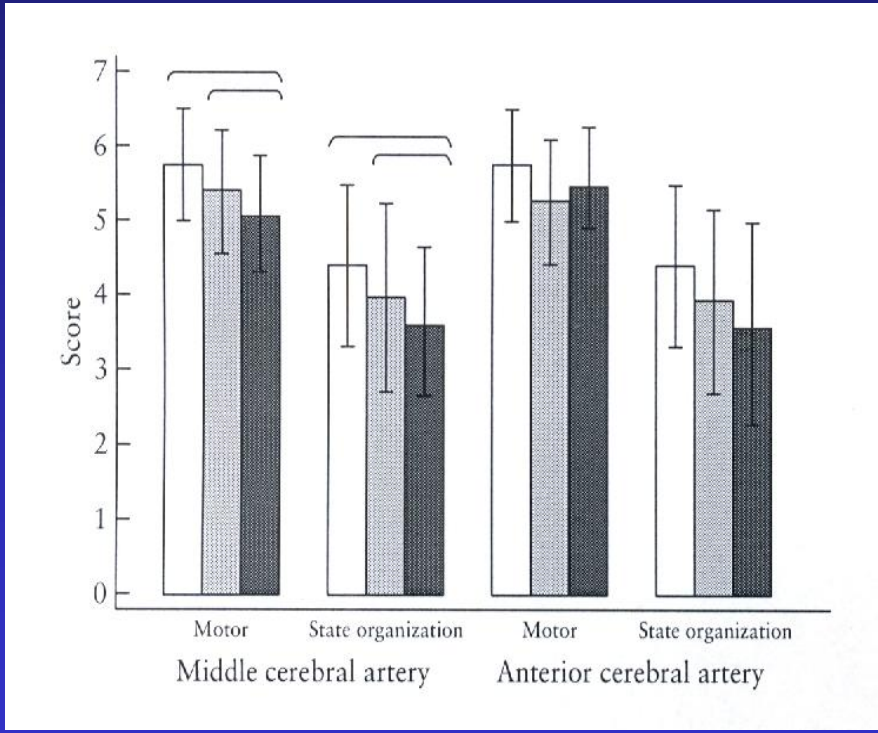
Figure 1 Frequency of intrapartum Cesarean delivery (CD), emergency CD due to non-reassuring fetal status (NRFS) and any period of neonatal hospitalization for controls and for small-for-gestational-age fetuses classified according to estimated fetal weight centile group. □, Controls; ▒, SGA ≥3rd centile;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

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

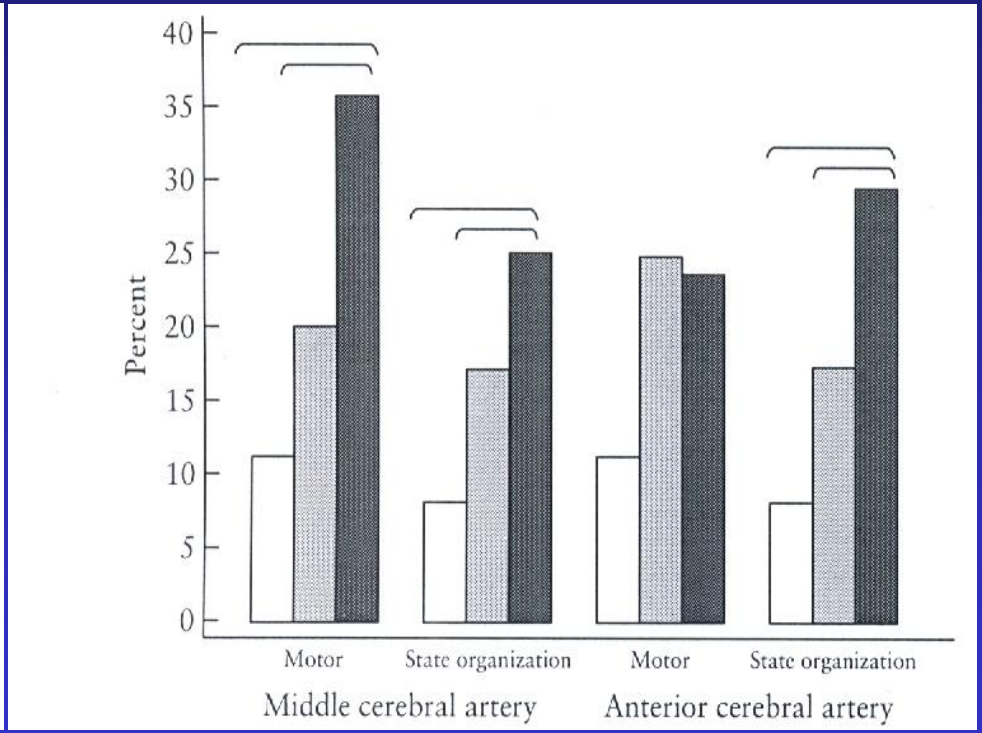
Savchev et al, UOG 2012

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

Neurobehavioral scores

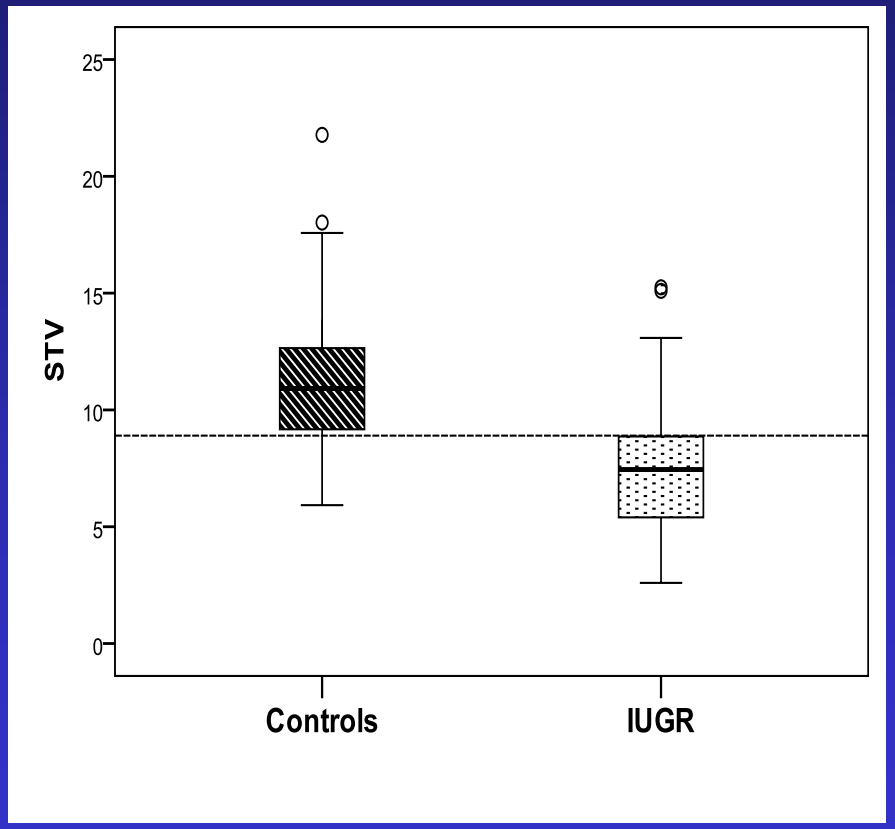


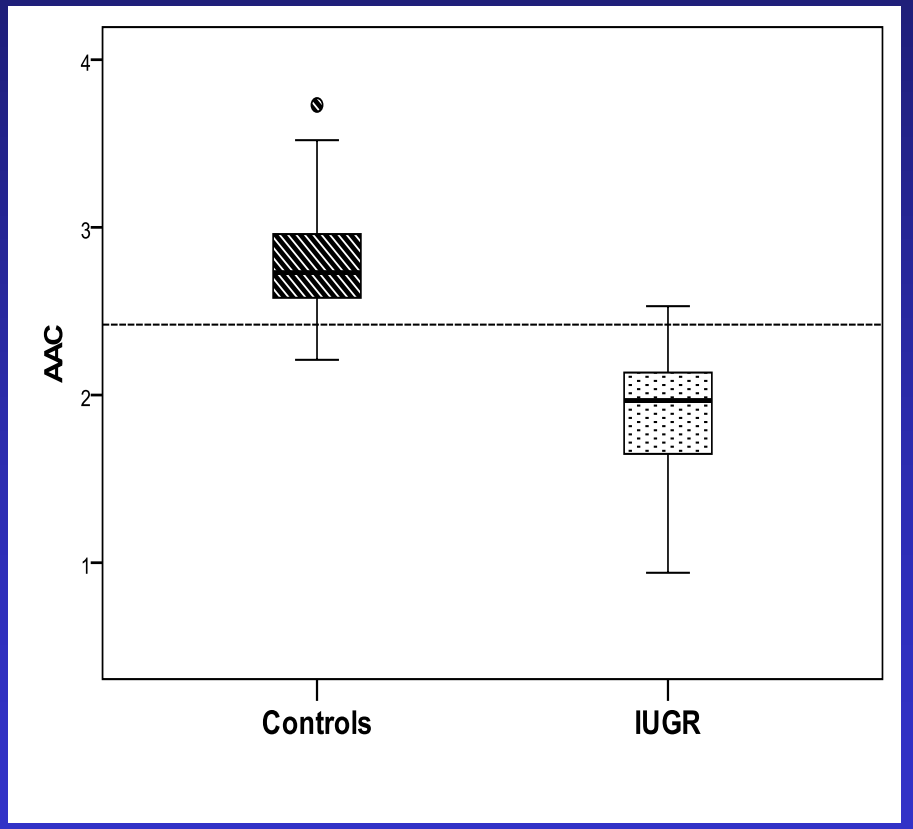
% abnormal neurobehavior



Oros et al, UOG, 2010

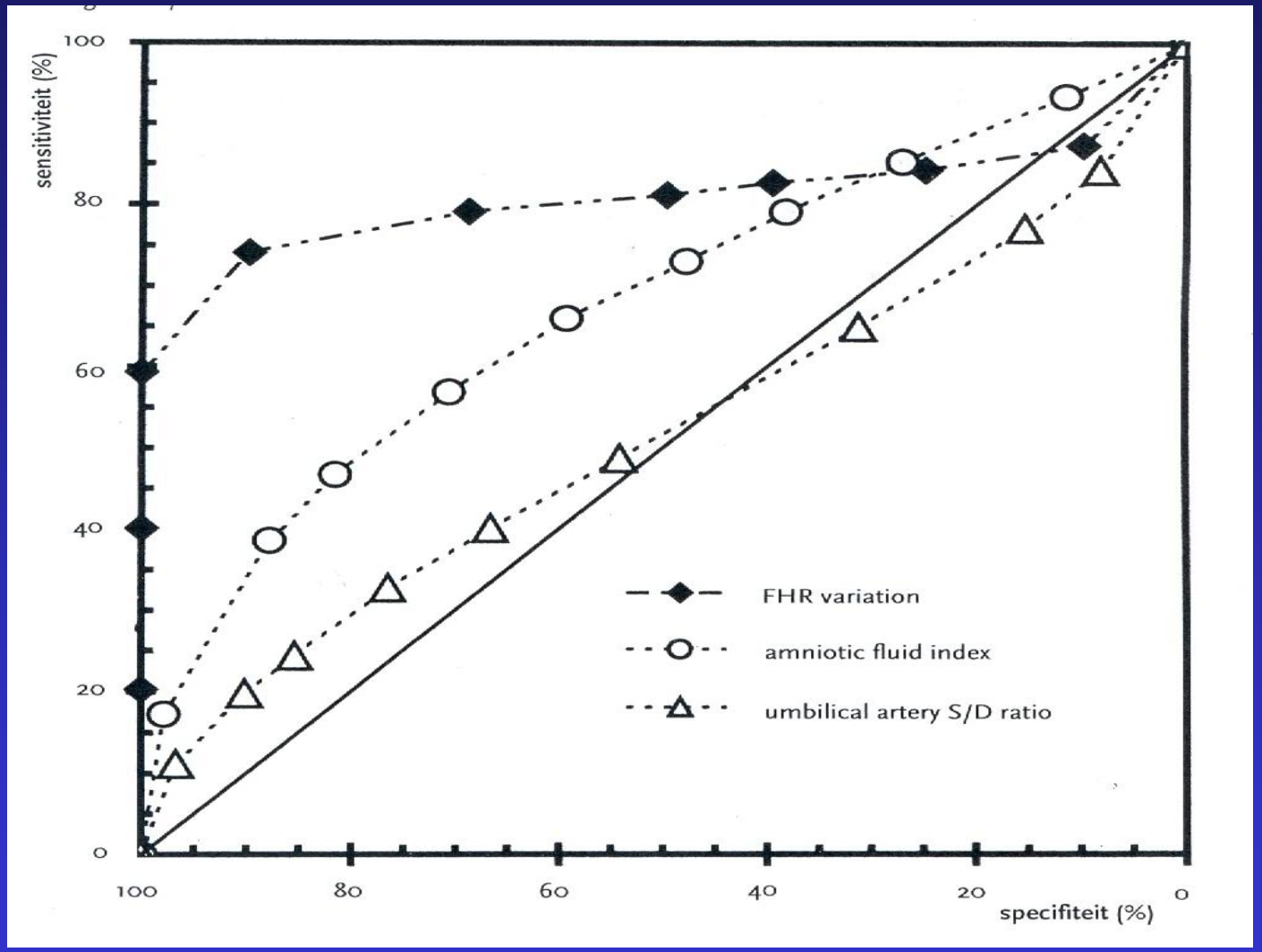
STV and Average Acceleration capacity in controls and IUGR





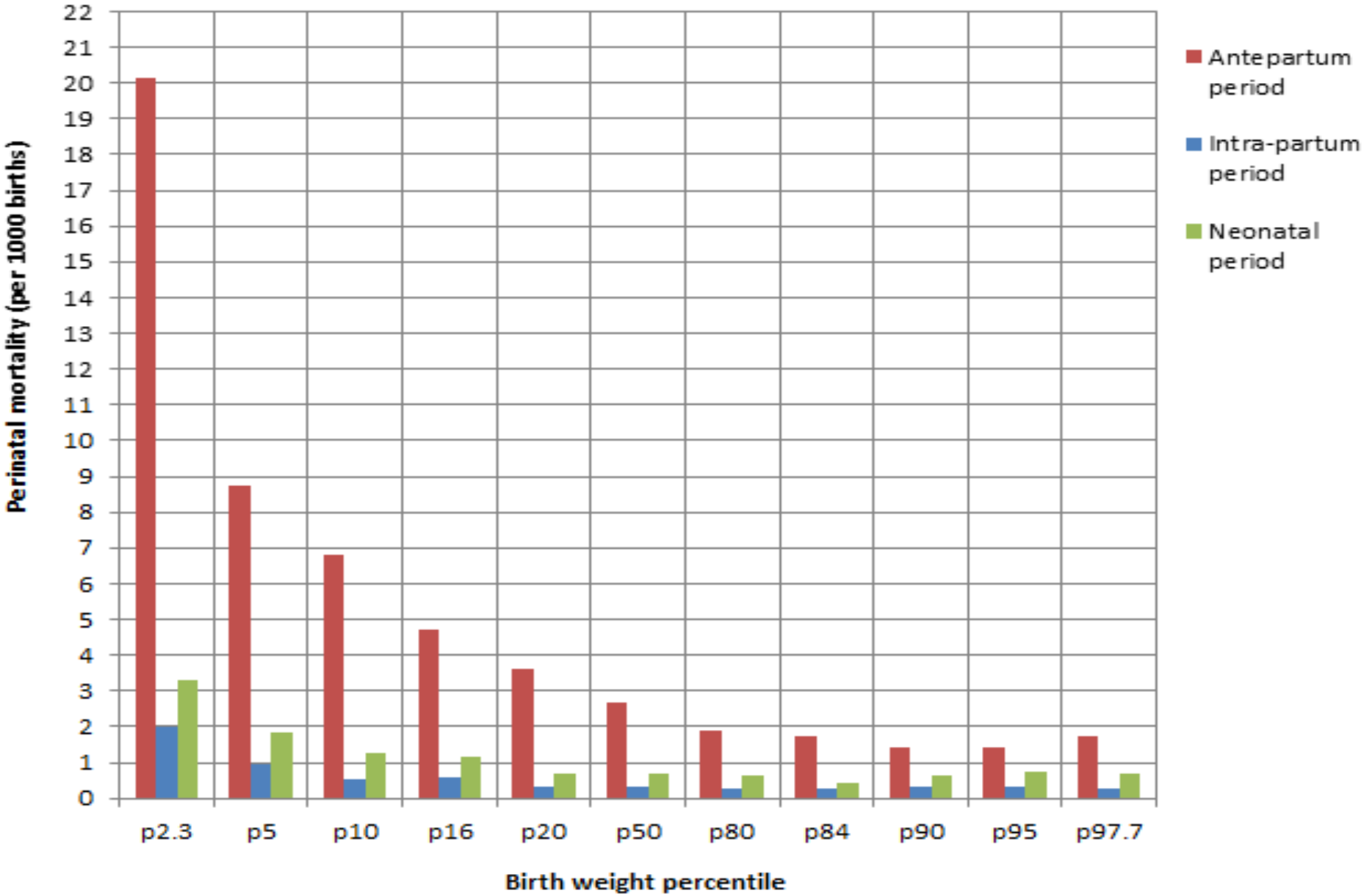
Lobmaier et al, 2010

FHR, Amniotic fluid and Doppler Umb art, 41 wks

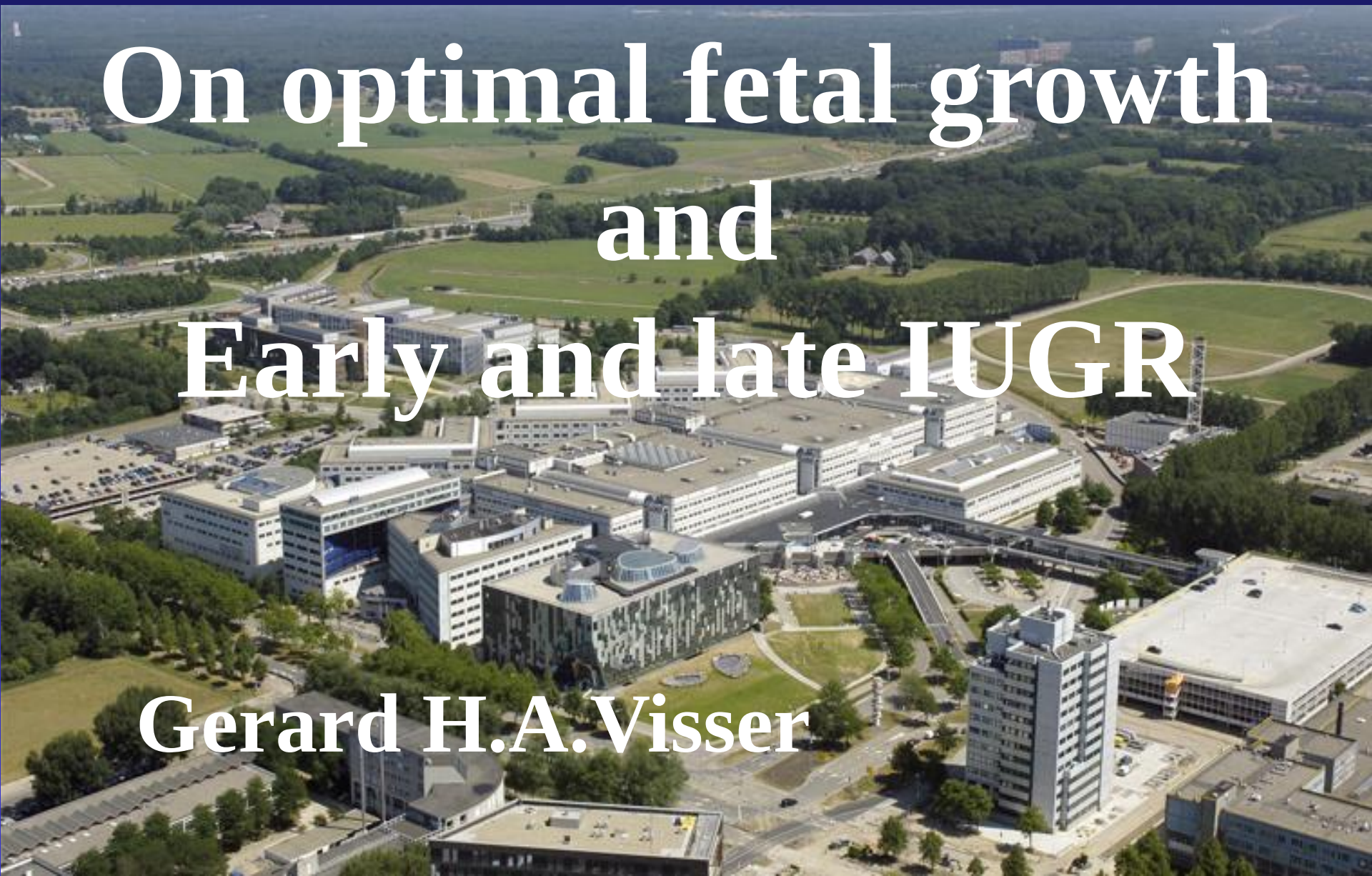


N=367, Weiner et al, AJOG, 1994

Perinatal mortality>28 wks



University Medical Center, Utrecht, the NL



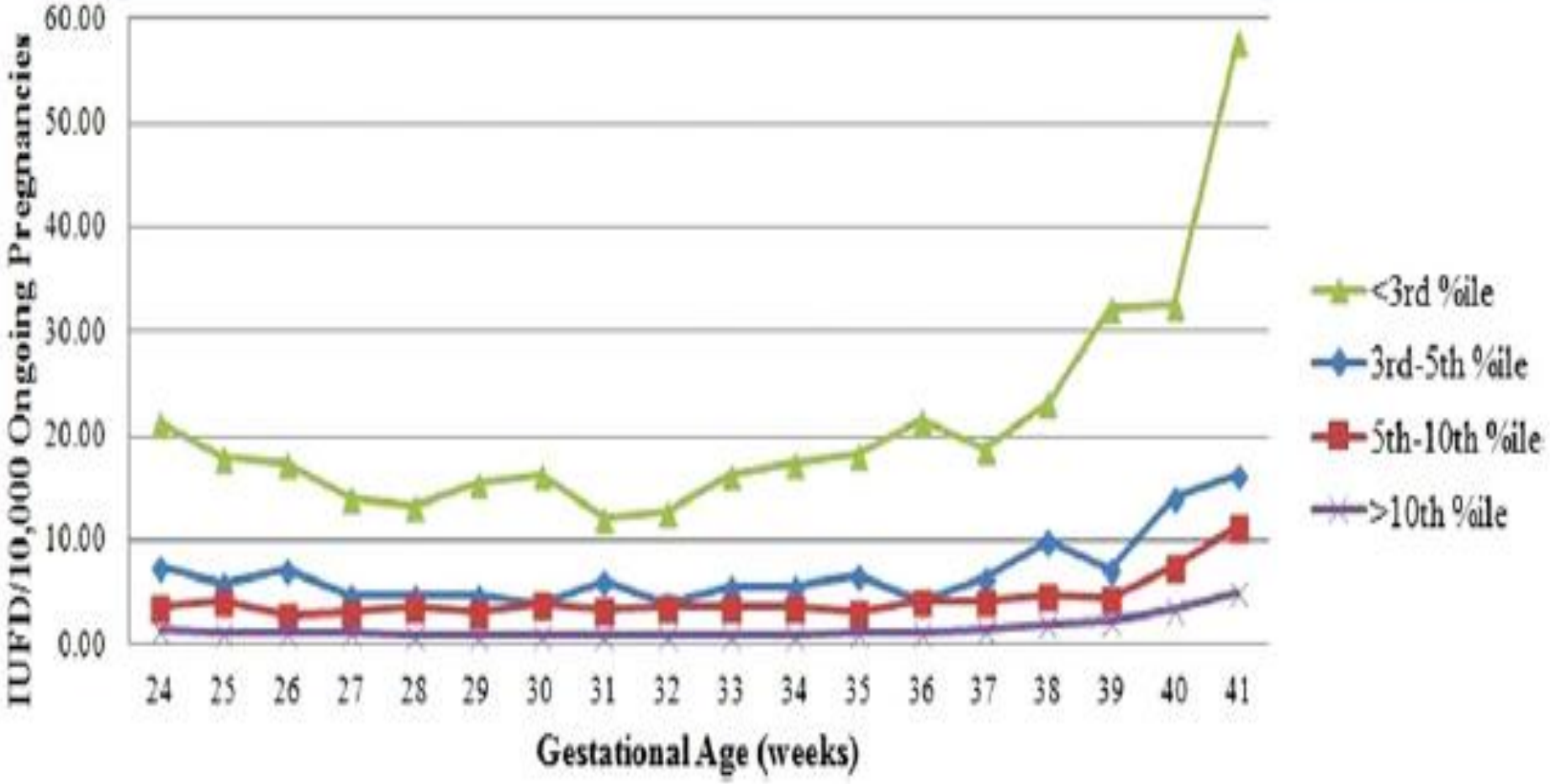
On optimal fetal growth and Early and late IUGR

Gerard H.A.Visser

FIGURE

Risk of IUFD by gestational age

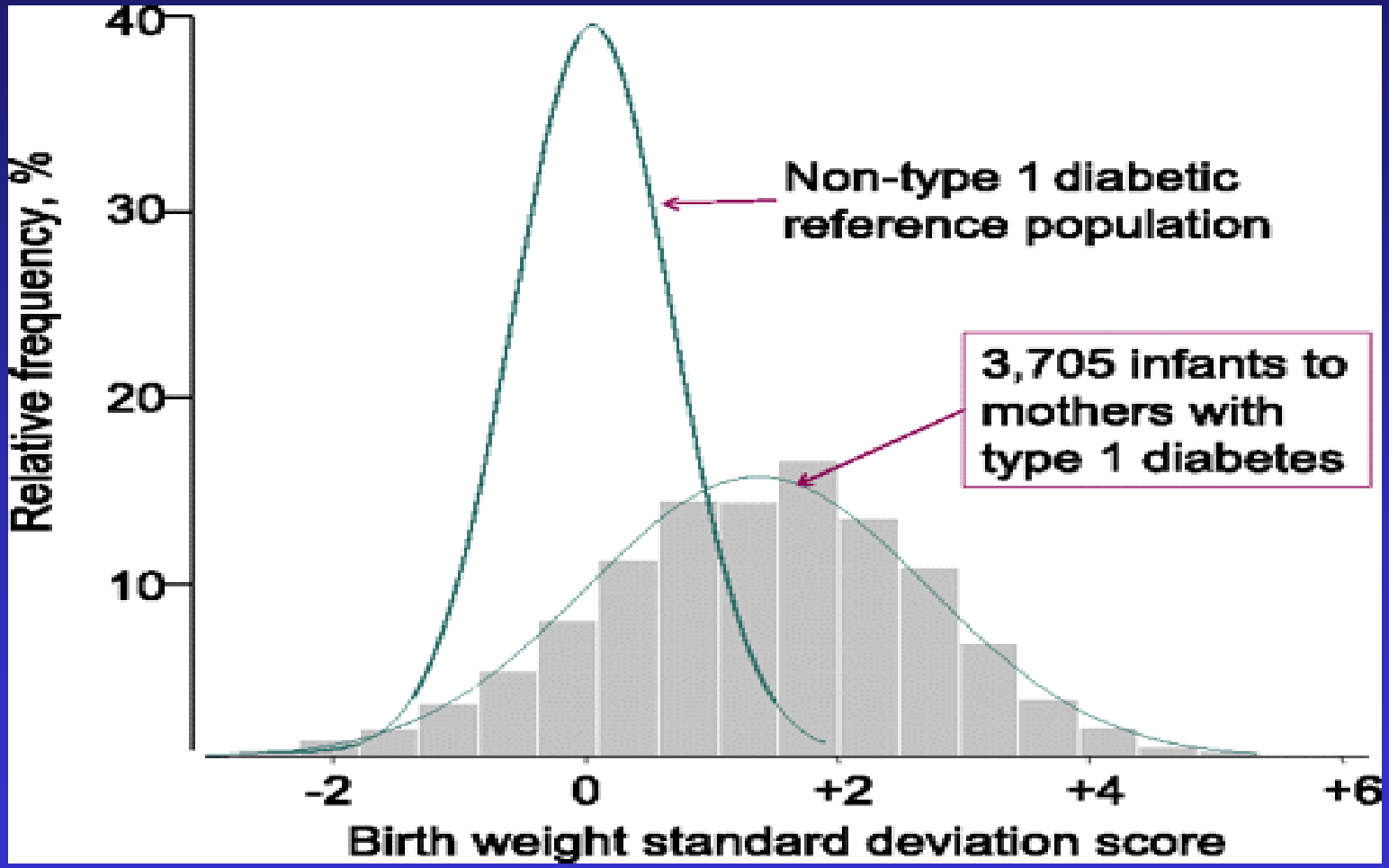
Nationwide data USA 2005



IUFD, intrauterine fetal death.

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

Birth weight distribution



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

On optimal fetal growth:

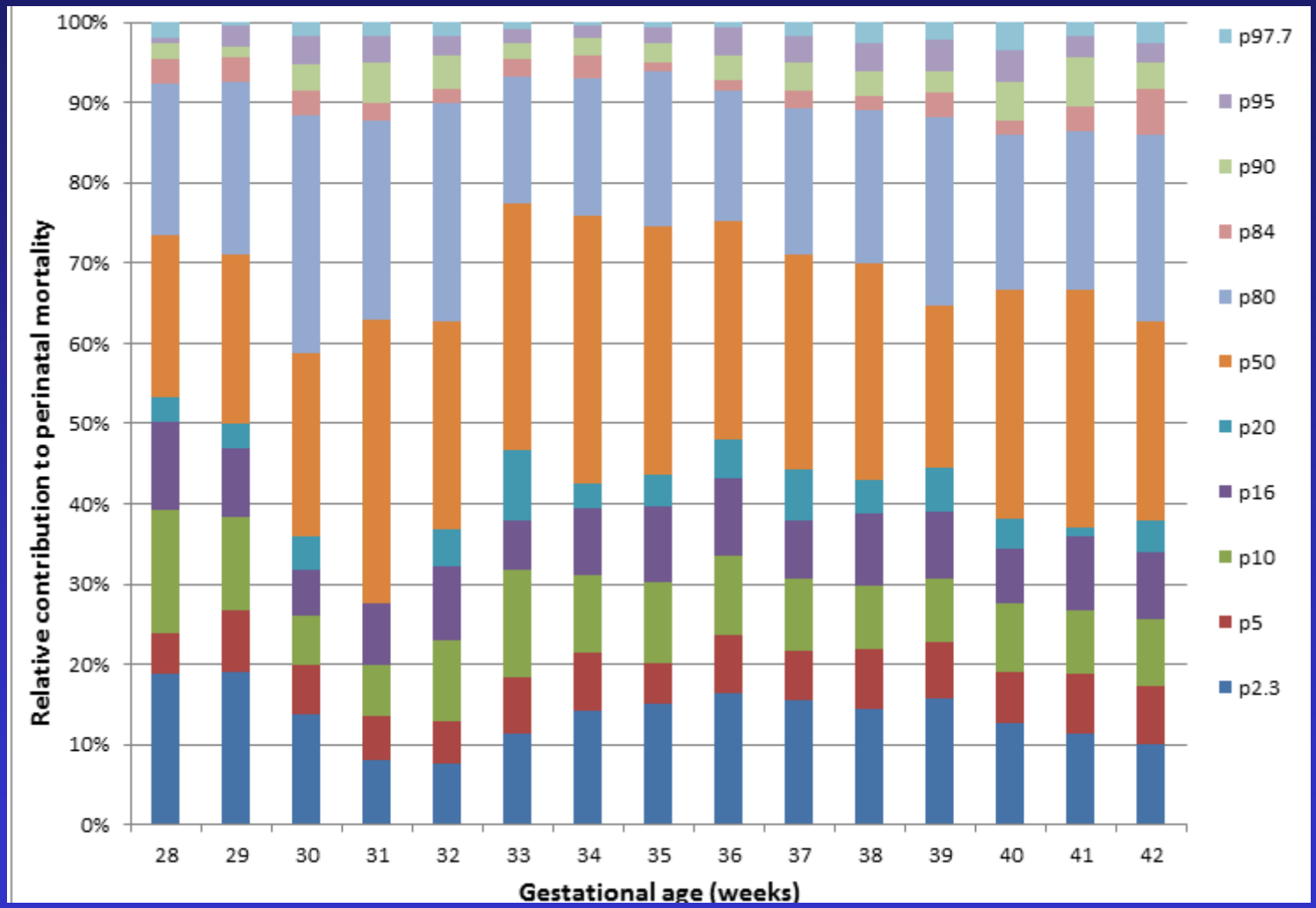
Which birth weight centiles are associated with the lowest perinatal mortality

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

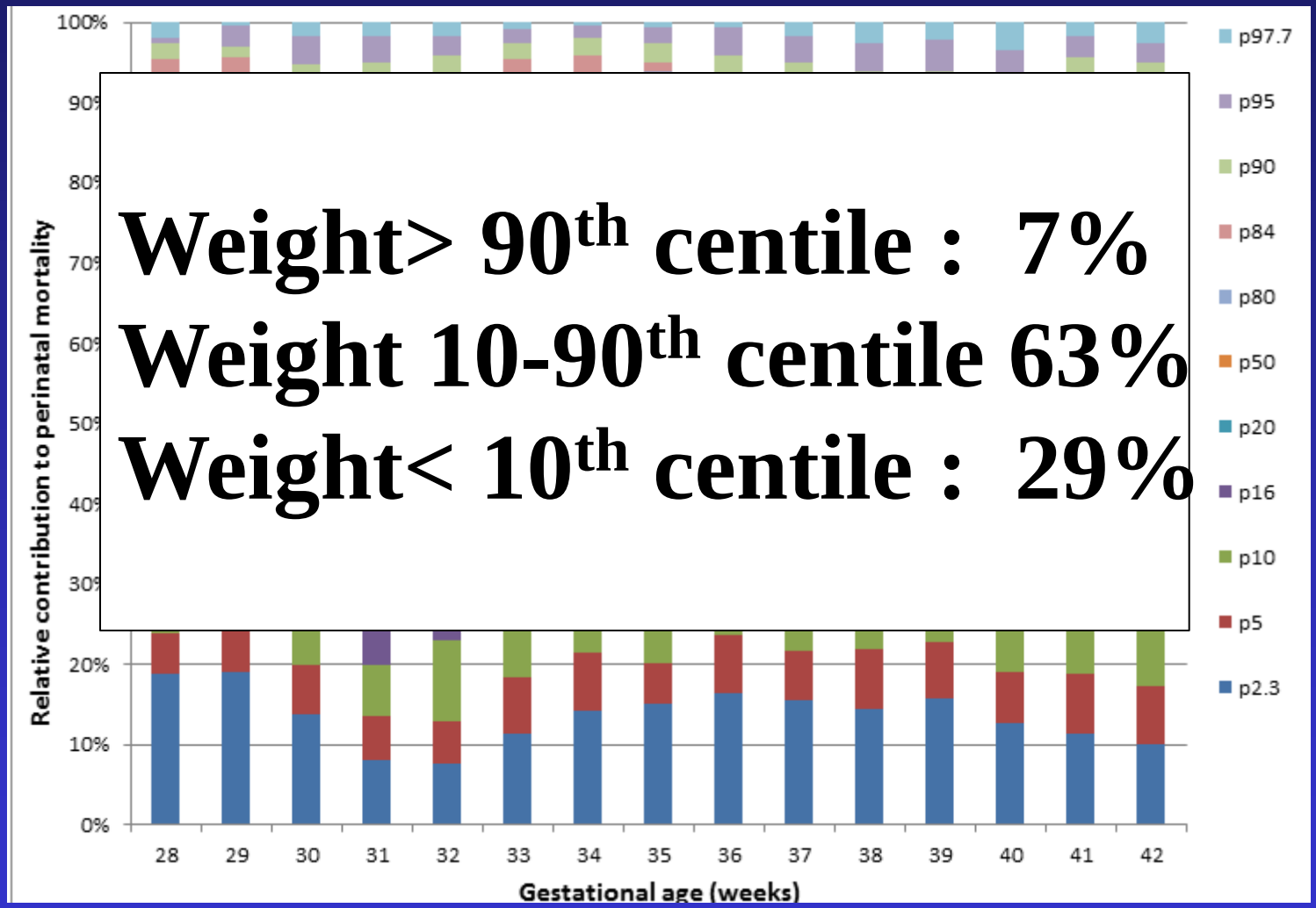
- N=1.170.127 PNM 5.048 (0.4%)

Vasak et al, in preparation

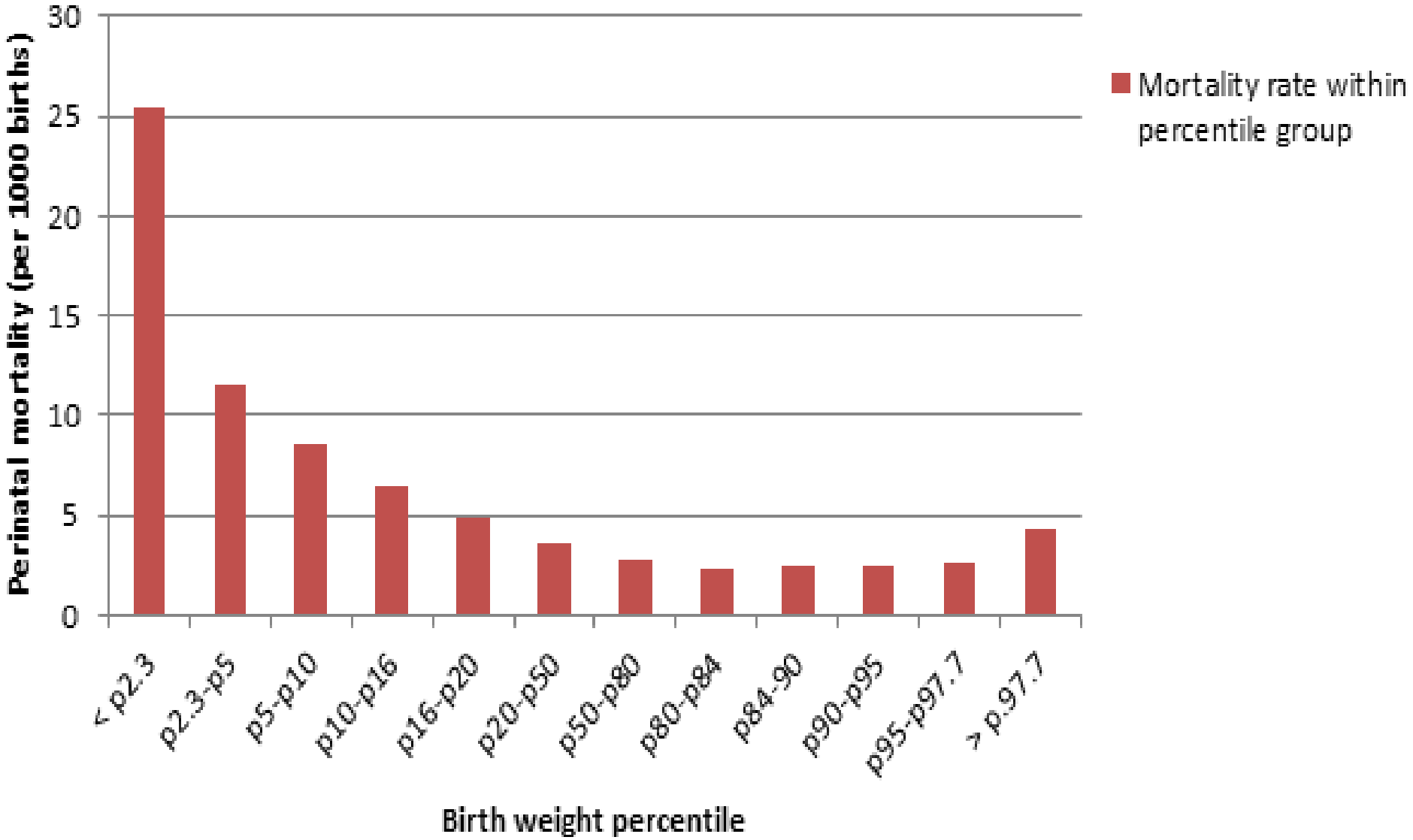
Contribution of the different birt weight centile groups to perinatal mortality



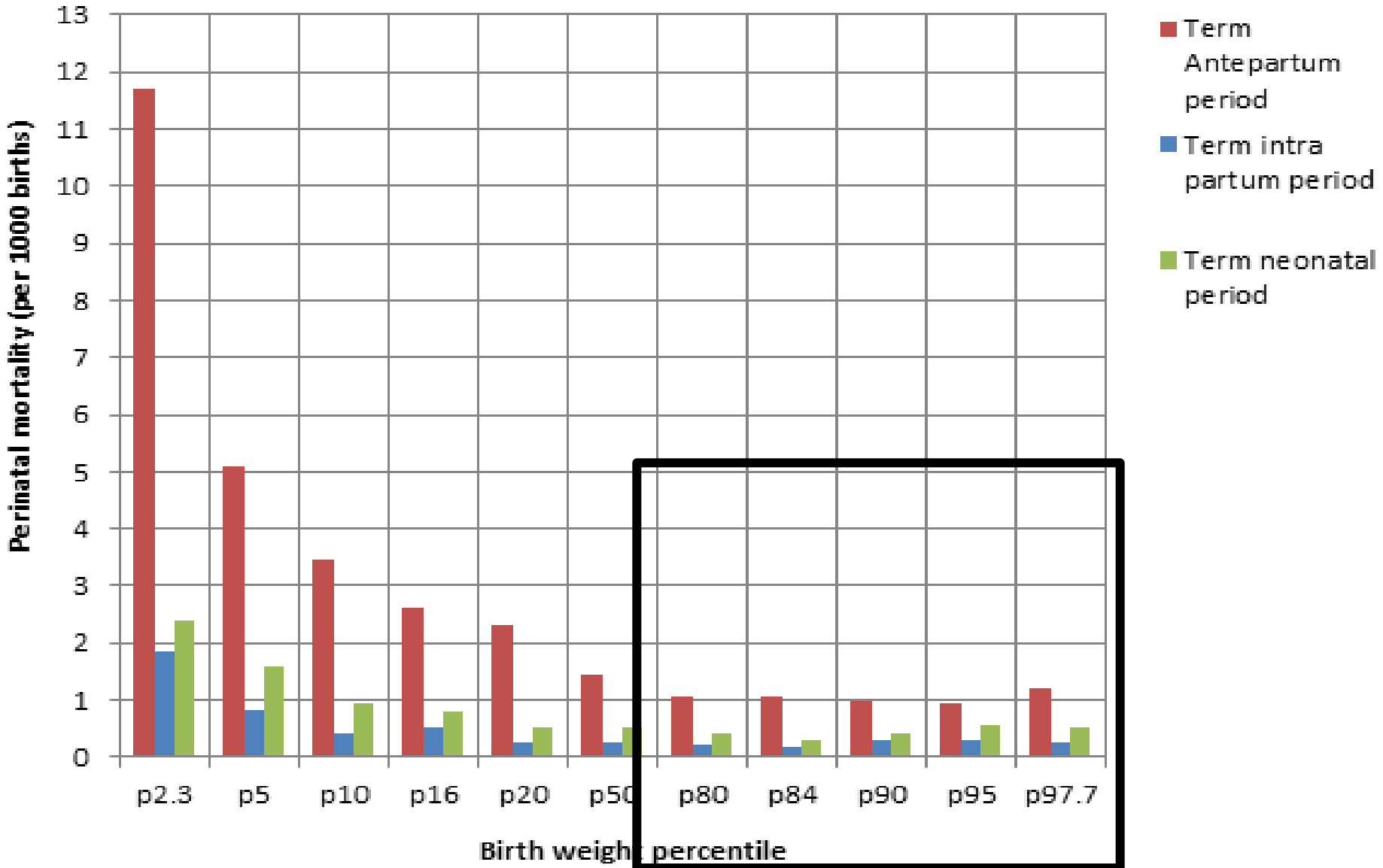
Contribution of the different birt weight centile groups to perinatal mortality



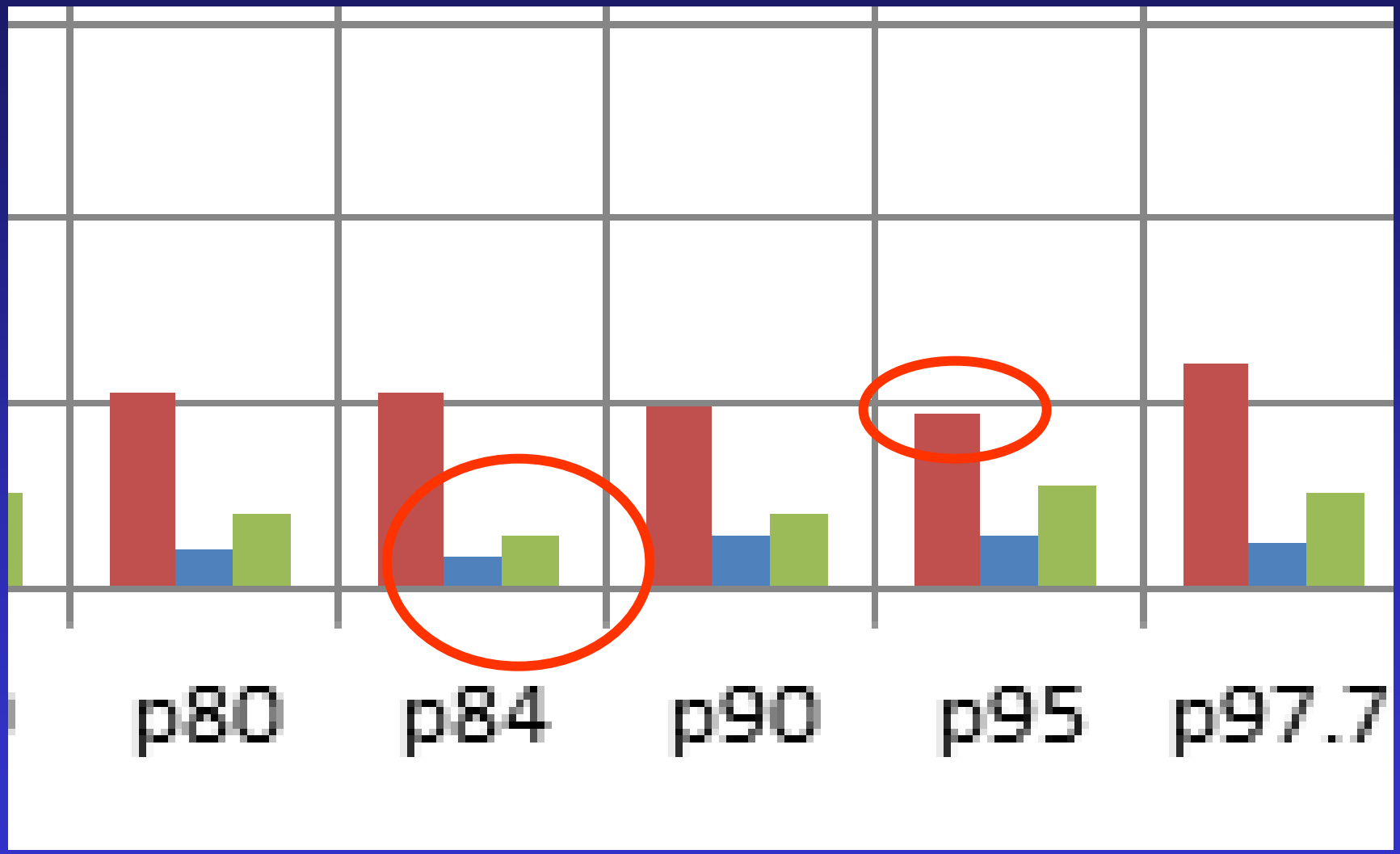
Perinatal mortality >28 wks, Nlds 2000-2008



Perinatal mortality >= 36 wks



Perinatal mortality >= 36 wks



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?

Human fetal growth is restrained below optimal for fetal survival

Since 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

1342 Stillbirths > 28 wks gestation; UK

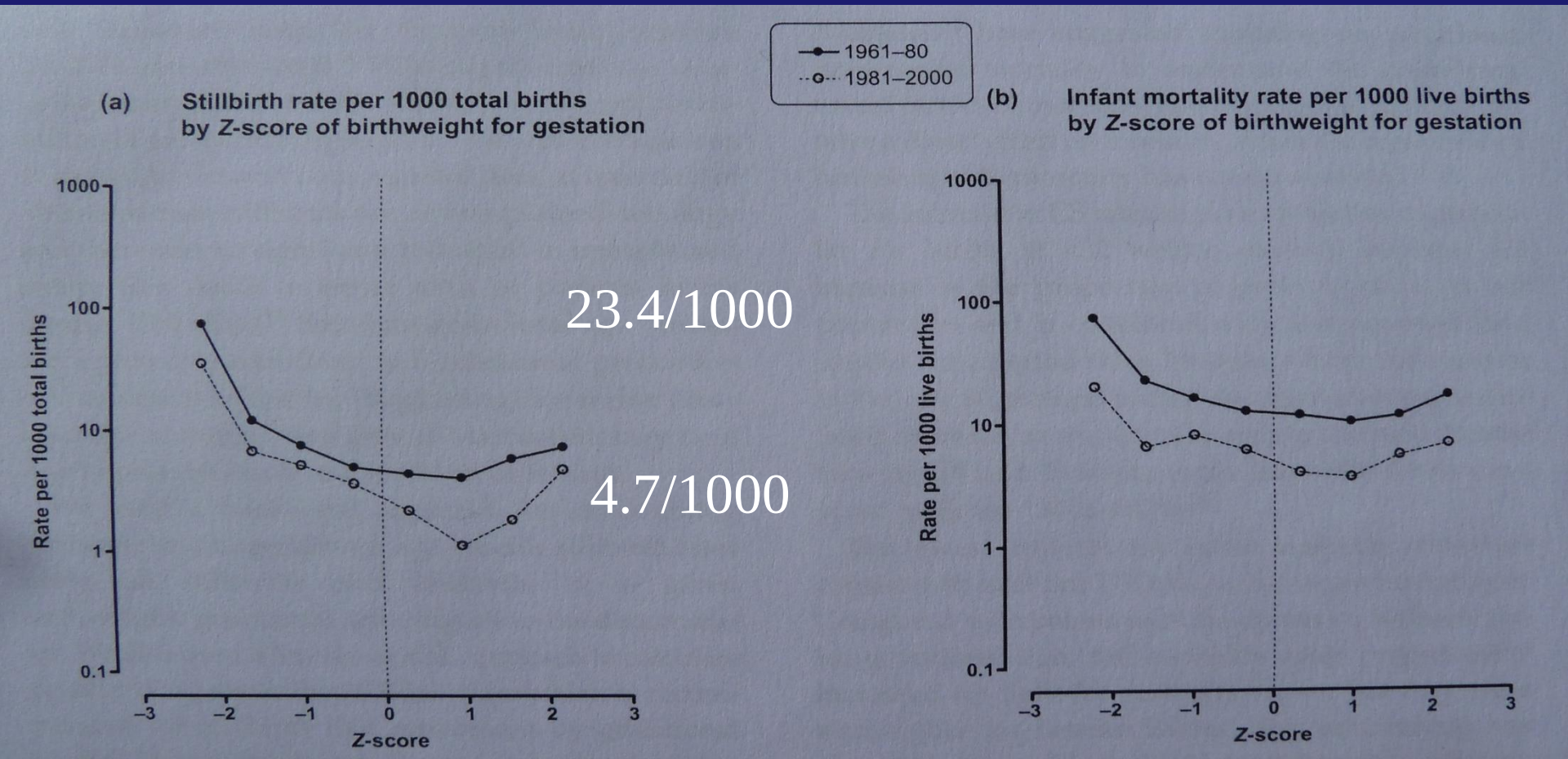


Figure 3. (a) Stillbirth and (b) infant mortality rates (on a log scale) by Z-score of birthweight-for-gestation in singleton births in 1961–80 and 1981–2000, Newcastle upon Tyne.

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

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

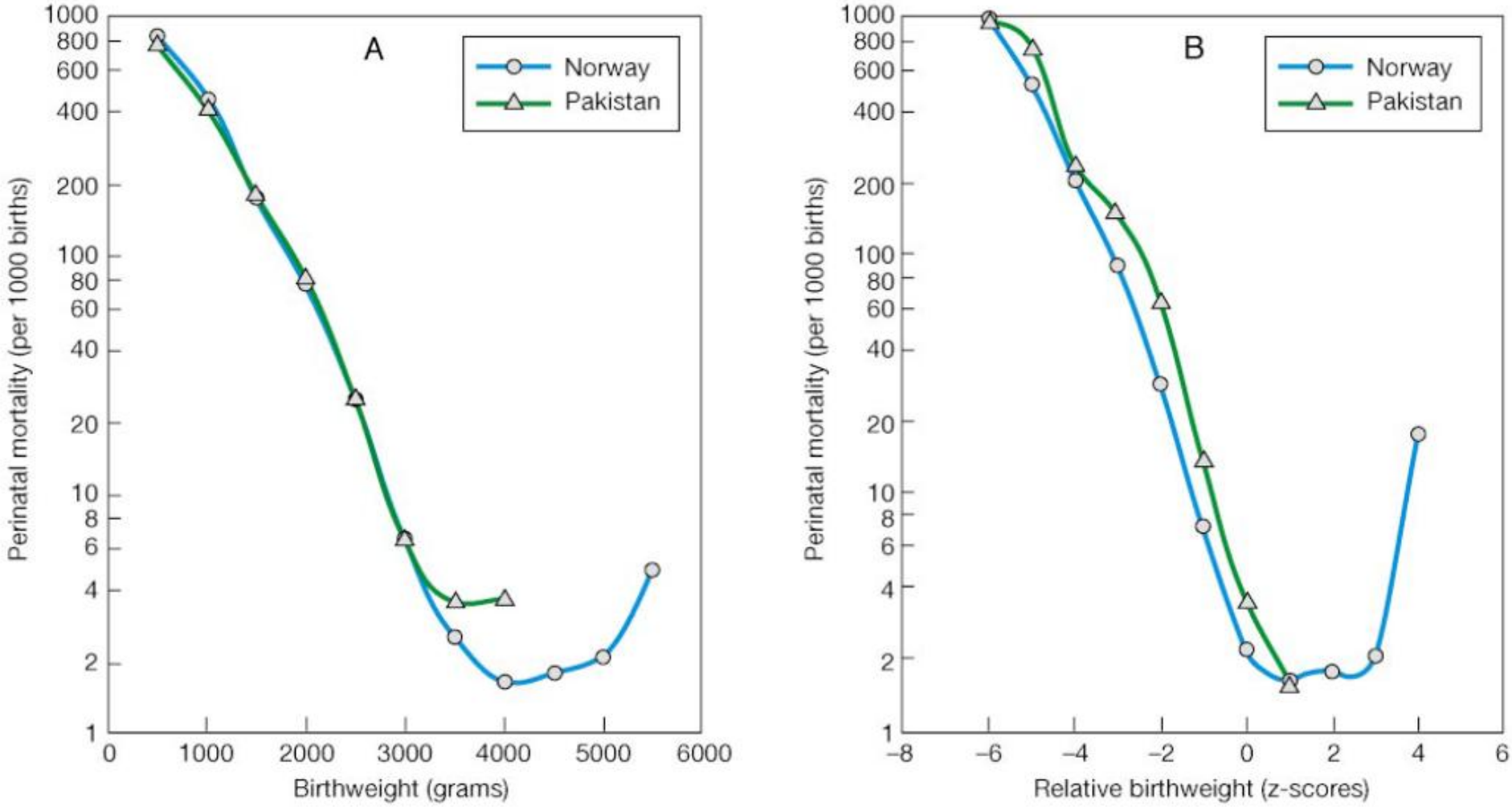


Figure 2 Birthweight-specific mortality before (A) and after (B) adjustment to a relative birthweight scale for Pakistani and Norwegian births, Norway 1980–1995

Vangen et al, Int J Epidemiol 2002

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

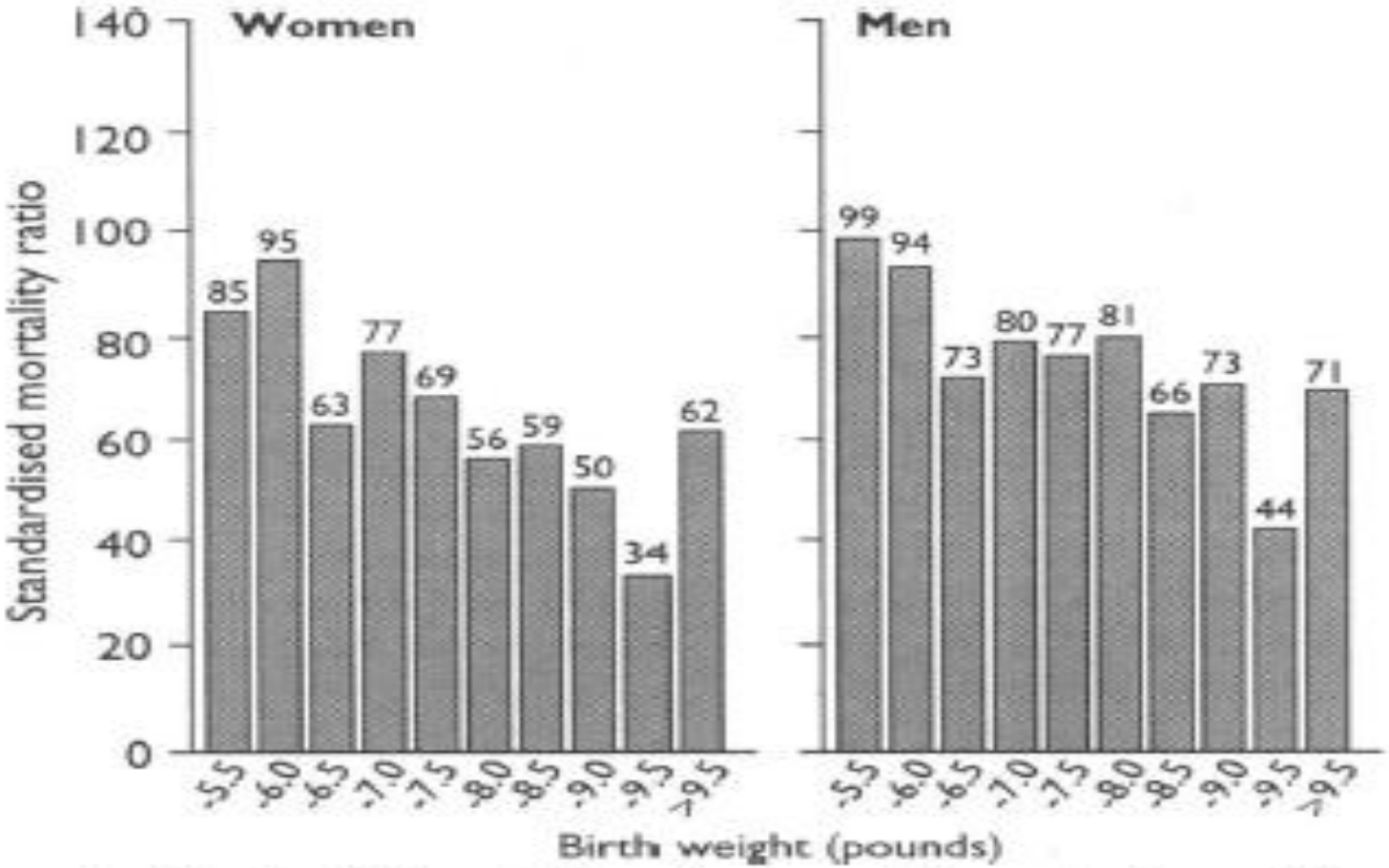


FIG 1—*Standardised mortality ratios for cardiovascular disease below age of 65 according to birth weight*

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.

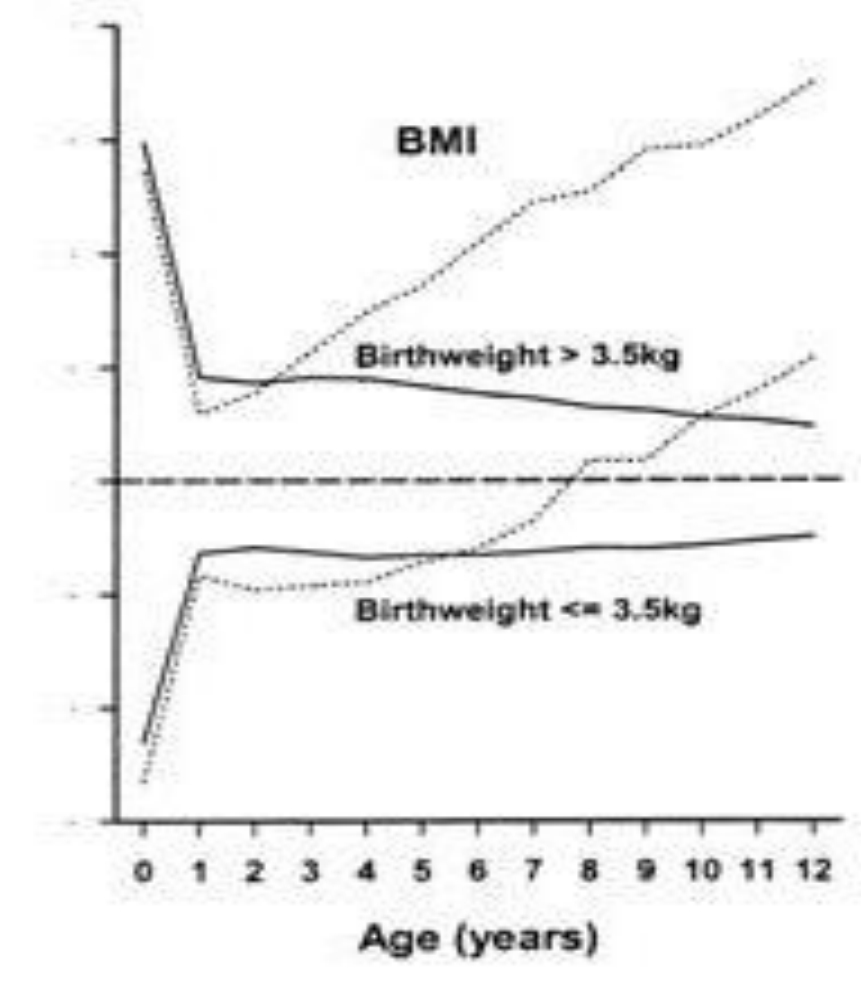
Lawlor et al, Circulation 2005

So, for short and long term survival

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

Birthweight, Infant growth & Type-2 diabetes

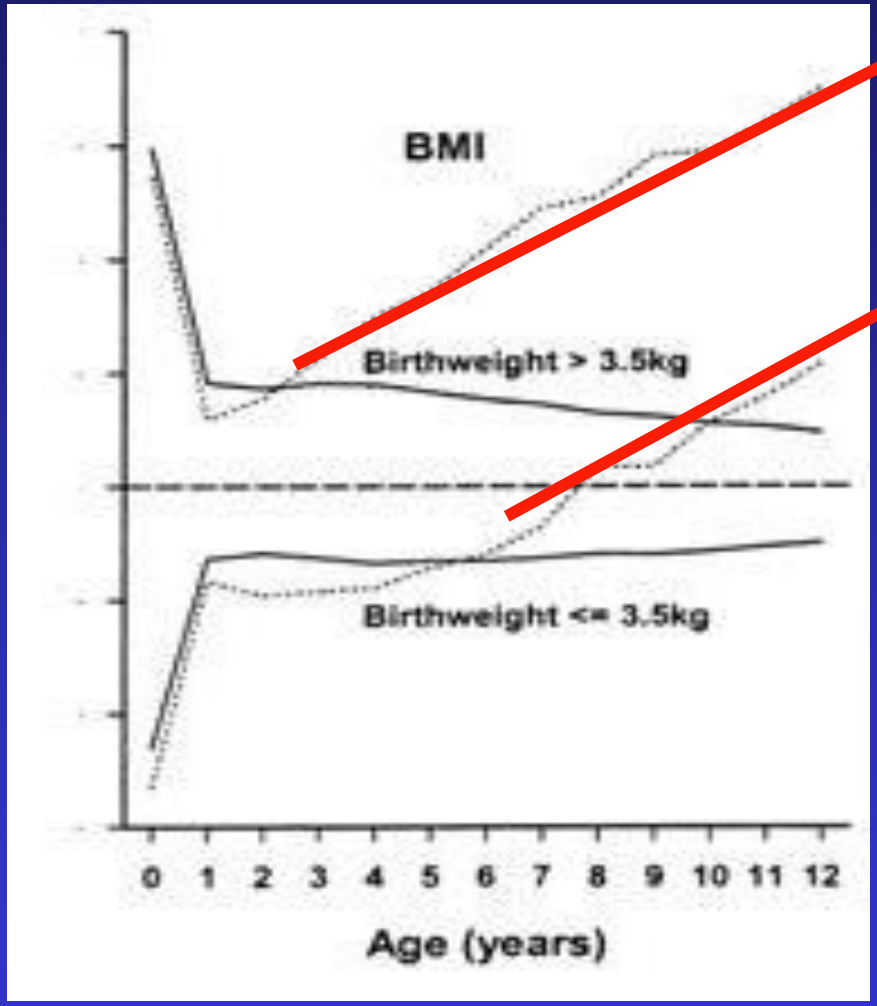
Mean Z-score



(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

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