University Medical Center, Utrecht, the NL

# Fetal Growth Restriction

## Detection and management

**Gerard H.A. Visser**

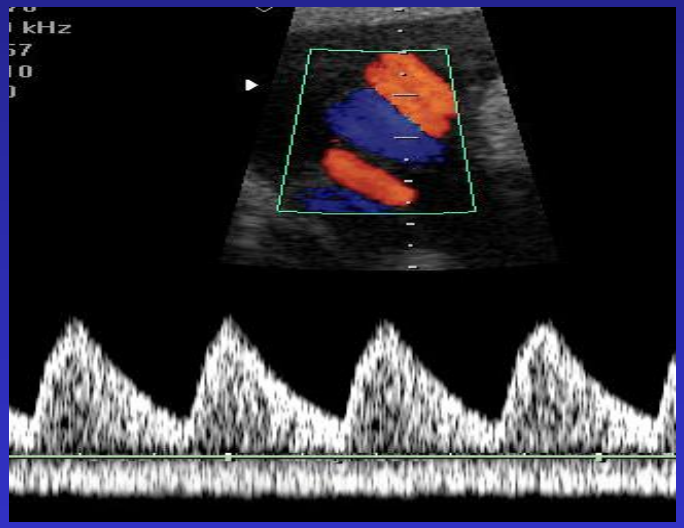
**Chair FIGO Committee Safe Motherhood & Newborn Health**

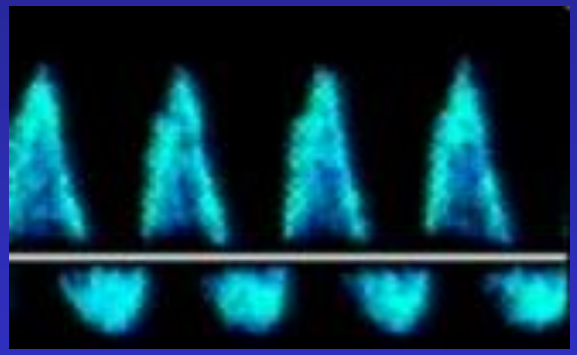
FIGO International Federation of Gynecology and Obstetrics

# 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, for early IUGR…

- Easy identification
- Sufficient monitoring tools

- But,….. what next??
- Therapy: Oxygen?

  Corticosteroids?

  Neuroprevention ( $MgSO_4$, Allopurinol)

  Sildenafil ( Viagra) Sharp et al, Lancet ChAdH, 2017

# So, for the time being….

- Easy identification
- Sufficient monitoring tools

- So,….. for the time being

  The only option is (timing of) delivery (GRIT study*, …TRUFFLE study)

Thornton et al Lancet 2004, Walker et al AJOG 2011

# Early IUGR

**To karyotype or not to karyotype?**

- 458 referred cases of IUGR
- 19% abnormal karyotype
- < 26 wks: Triploidy; after 26 weeks Trisomy 18
- 96% had multisystem fetal defects
- N or incr AFV: 40% Abn Karyotype, reduced 8%
- N Dopplers Ut/Umb 44% abn Karyot, abnorm 8%

Normal fetal scan:<1% risk of chrom anomaly

Snijders RJ et al AJOG, 1993

# To TORCH or not to TORCH

## Is Infection screening indicated in GR fetuses?

J Obstet Gynaecol Res. 2013 Mar;39(3):653-7. doi: 10.1111/j.1447-0756.2012.02012.x. Epub 2012 Oct 29.

**Significance of maternal screening for toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus infection in cases of fetal growth restriction.**

Yamamoto R[1], Ishii K, Shimada M, Hayashi S, Hidaka N, Nakayama M, Mitsuda N.

⊕ Author information

**Abstract**

**AIM:** The objective of this study was to evaluate the significance of maternal toxoplasmosis, rubella, cytomegalovirus (CMV) and herpes simplex virus (TORCH) screening in cases of fetal growth restriction (FGR).

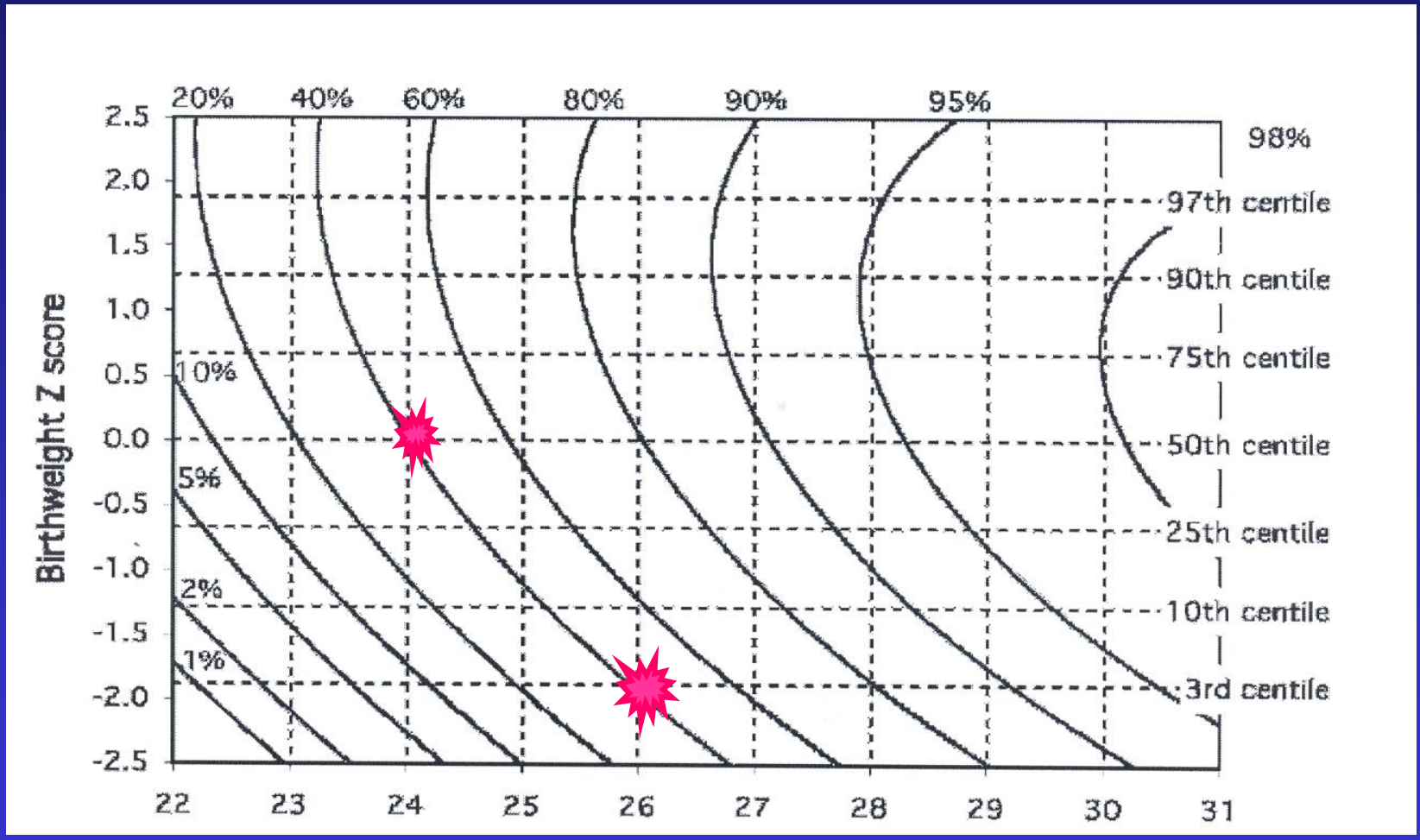
**MATERIAL AND METHODS:** The medical records of women carrying fetuses with FGR who underwent TORCH screening over a 10-year period were retrospectively reviewed for maternal and congenital TORCH infection. Women carrying fetuses with FGR routinely underwent serologic TORCH tests and systematic ultrasound evaluation for congenital abnormalities. If a congenital CMV infection was suspected, amniotic fluid, placenta or neonatal urine was used for CMV DNA detection by polymerase chain reaction.

**RESULTS:** In 319 patients, no cases of maternal or congenital infection with toxoplasma, rubella, or herpes simplex virus were found. Conversely six cases (1.8%) were diagnosed with congenital CMV infection, two of which had no structural abnormalities other than FGR.

**CONCLUSIONS:** A complete maternal TORCH screening for cases of FGR appears to be unnecessary. Although a maternal CMV test can be considered, the incidence of congenital CMV infection was found to be low in FGR cases.

CMV: 6 out of 319; 2 ( 0.6%)without struct. anomalies

# Prognosis early IUGR: PREM-score




Cole et al, Arch Dis Child Fetal Neonatal Ed 2010;95:F14-19

# Survival SFD/IUGR infants

- Comparable to that of  appropriate for dates infants with a 2 wks shorter gestational age

# Survival SFD/IUGR infants

- Comparable to that of  appropriate for dates infants with a 2 wks shorter gestational age

So ,if you would normally advocate an active management to try to keep the baby alive from 24 weeks onwards, you may decide to wait till 26 weeks (and/or>600g) in case of IUGR

# Timing of delivery of the early IUGR fetus

**< 26 wks**

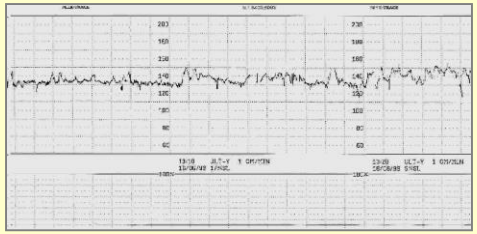
- Refrain from intervention?

Visser et al. IUGR survival at the limits of viability  Fetal Diagn Ther, 2014

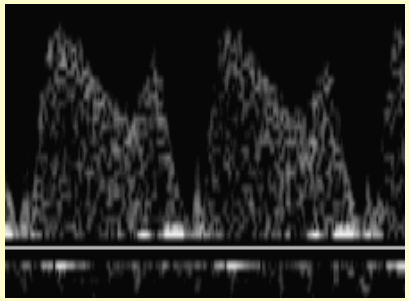
# *TRUFFLE Group*

## Randomized Management Study in IUGR

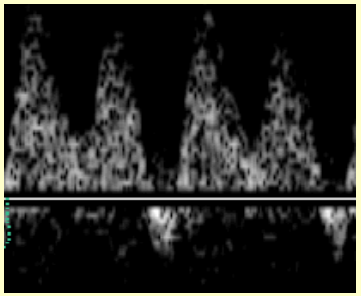
**Computerized CTG**



**Early ductus changes**



**Late ductus changes**



# *TRUFFLE Group*

***Inclusion*** 26-32 wks; AC<p10, PI Umb art>p95, EFW>500g

| **CTG STV** | **DV>p95** | **DV no A** |
|---|---|---|
| <3.5msec at<29wks<br>< 4msec > 29 wks | | |

**All groups as safety net: computerized CTG (STV<2.6msec <29wks or <3msec at 29-32wk), FHR decelerations, ReDF umb art >30 wks**
**Delivery> 32 wks, according to local protocol**

# Interval inclusion-delivery according to maternal disease

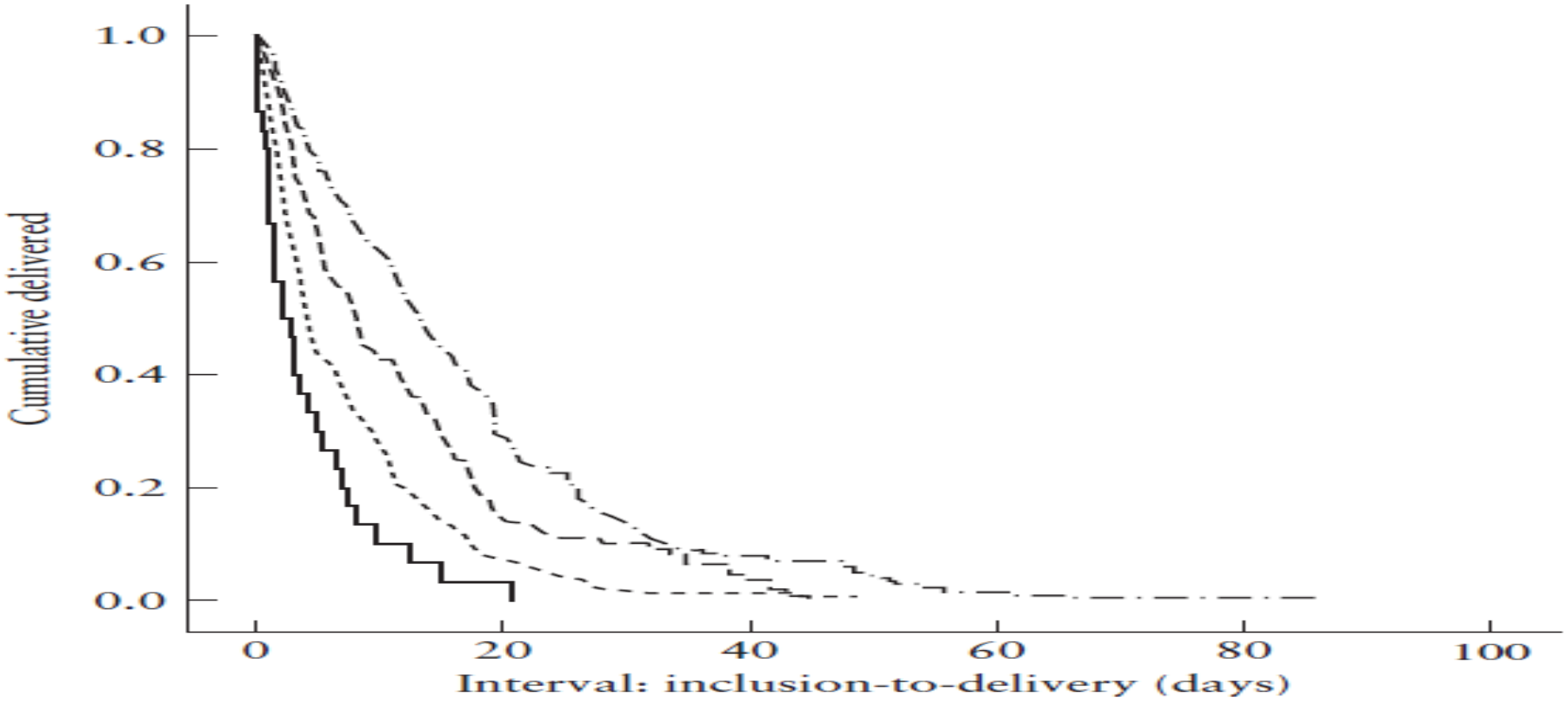
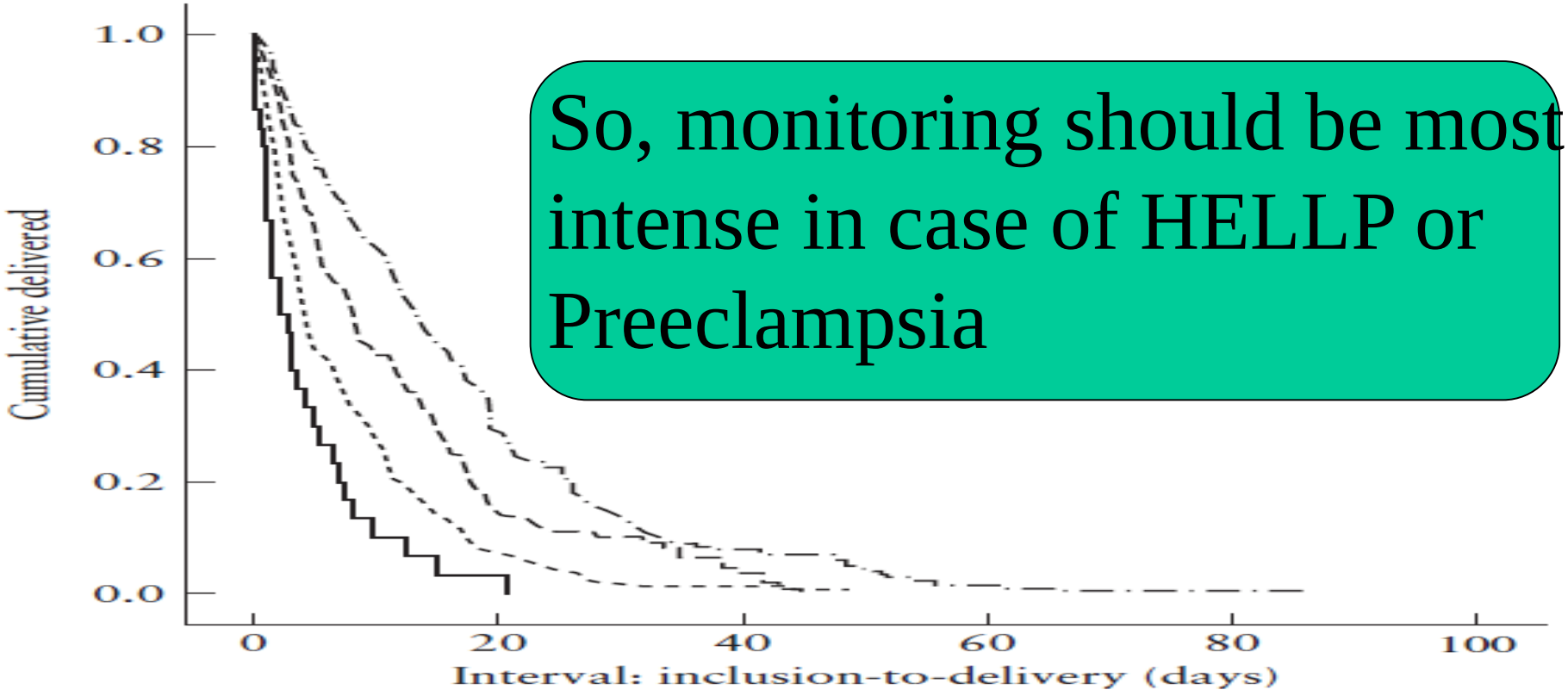



Figure 3 Kaplan–Meier analysis of interval between inclusion and delivery, presented separately for women with and those without hypertensive morbidity on inclusion. Differences between groups were statistically significant. ——, HELLP; - - - -, pre-eclampsia; – – – – –, gestational hypertension; — · —, no hypertensive morbidity.

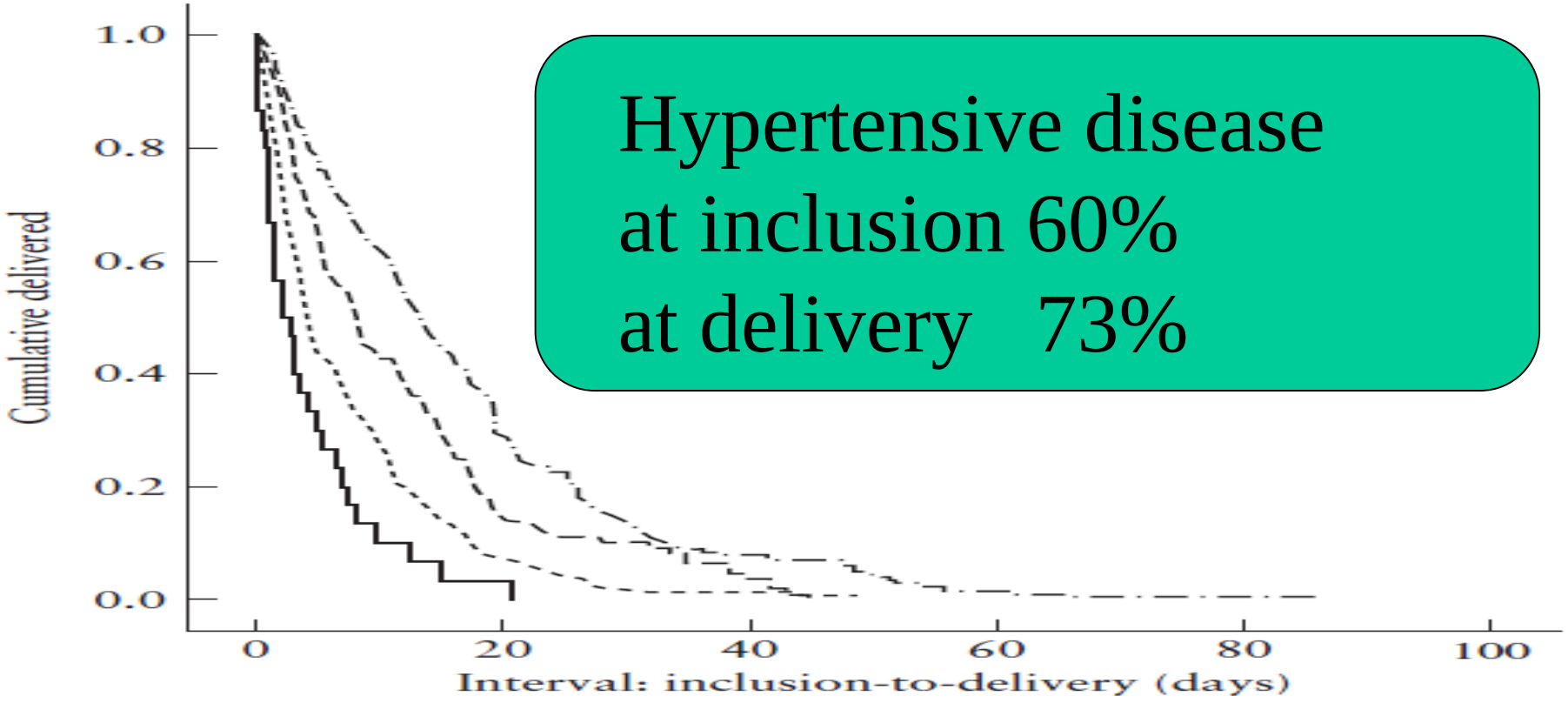
# Interval inclusion-delivery according to maternal disease




So, monitoring should be most intense in case of HELLP or Preeclampsia

Figure 3 Kaplan–Meier analysis of interval between inclusion and delivery, presented separately for women with and those without hypertensive morbidity on inclusion. Differences between groups were statistically significant. ——, HELLP; - - - -, pre-eclampsia; – – – – –, gestational hypertension; — · —, no hypertensive morbidity.

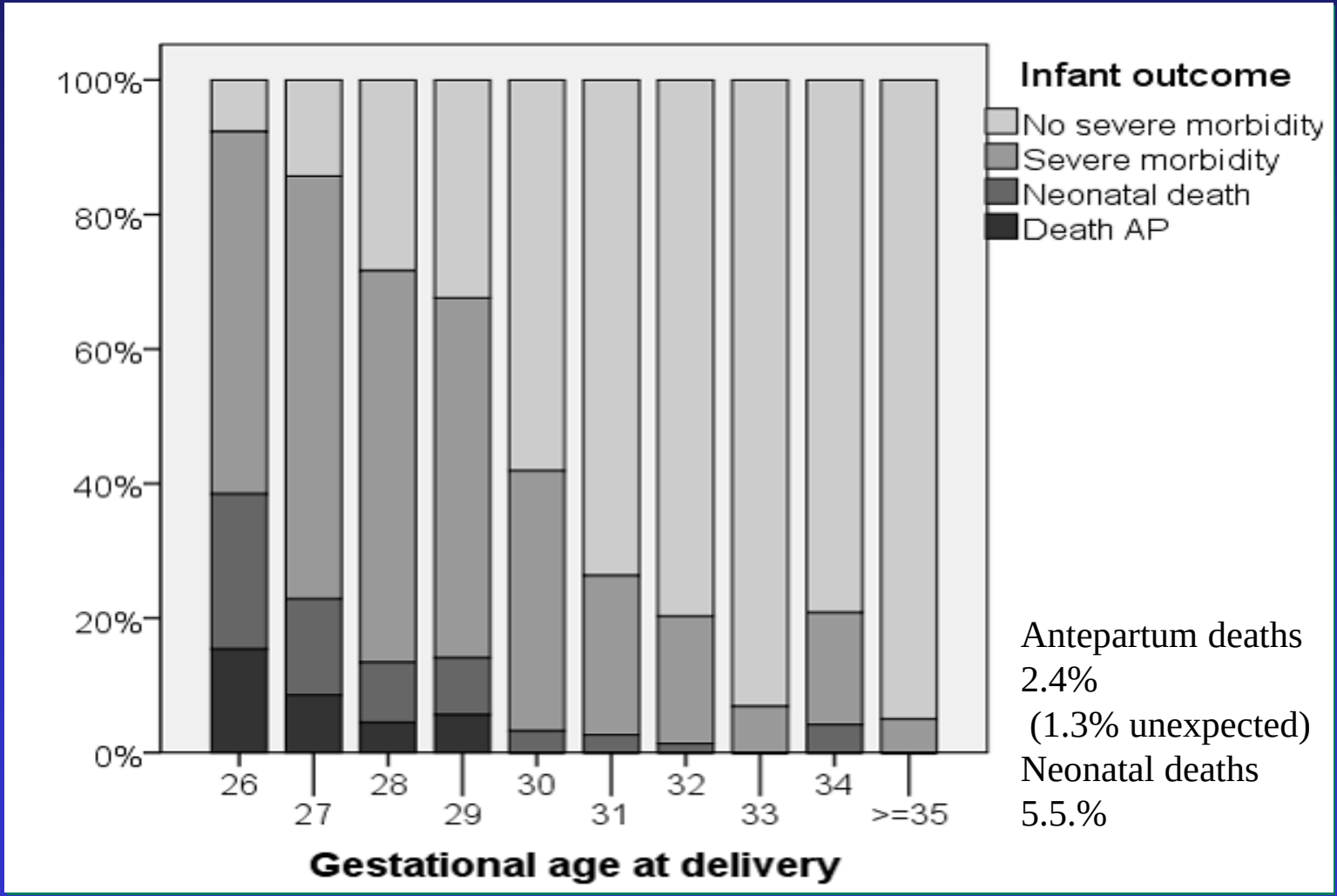
# Interval inclusion-delivery according to maternal disease




Hypertensive disease
at inclusion 60%
at delivery 73%

Figure 3 Kaplan–Meier analysis of interval between inclusion and delivery, presented separately for women with and those without hypertensive morbidity on inclusion. Differences between groups were statistically significant. ——, HELLP; - - - -, pre-eclampsia; – – – – –, gestational hypertension; — · —, no hypertensive morbidity.

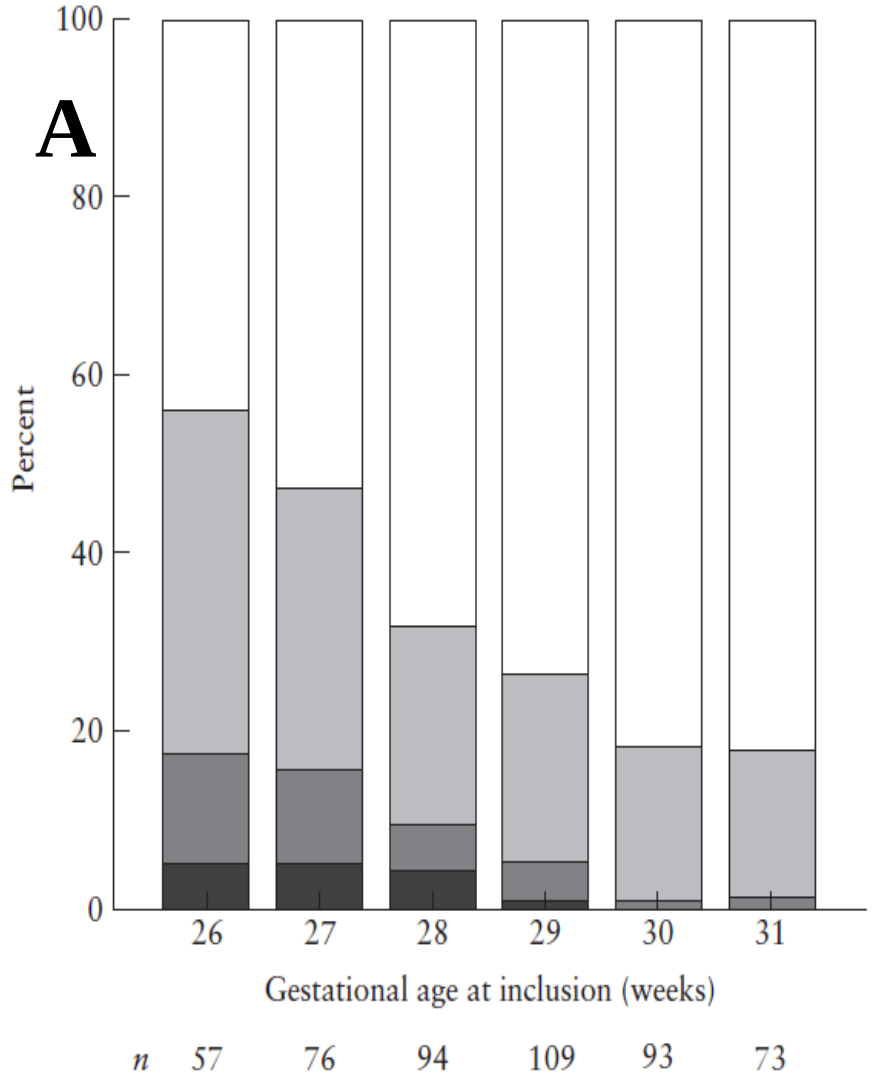
# TRUFFLE, Perinatal death & Morbidity

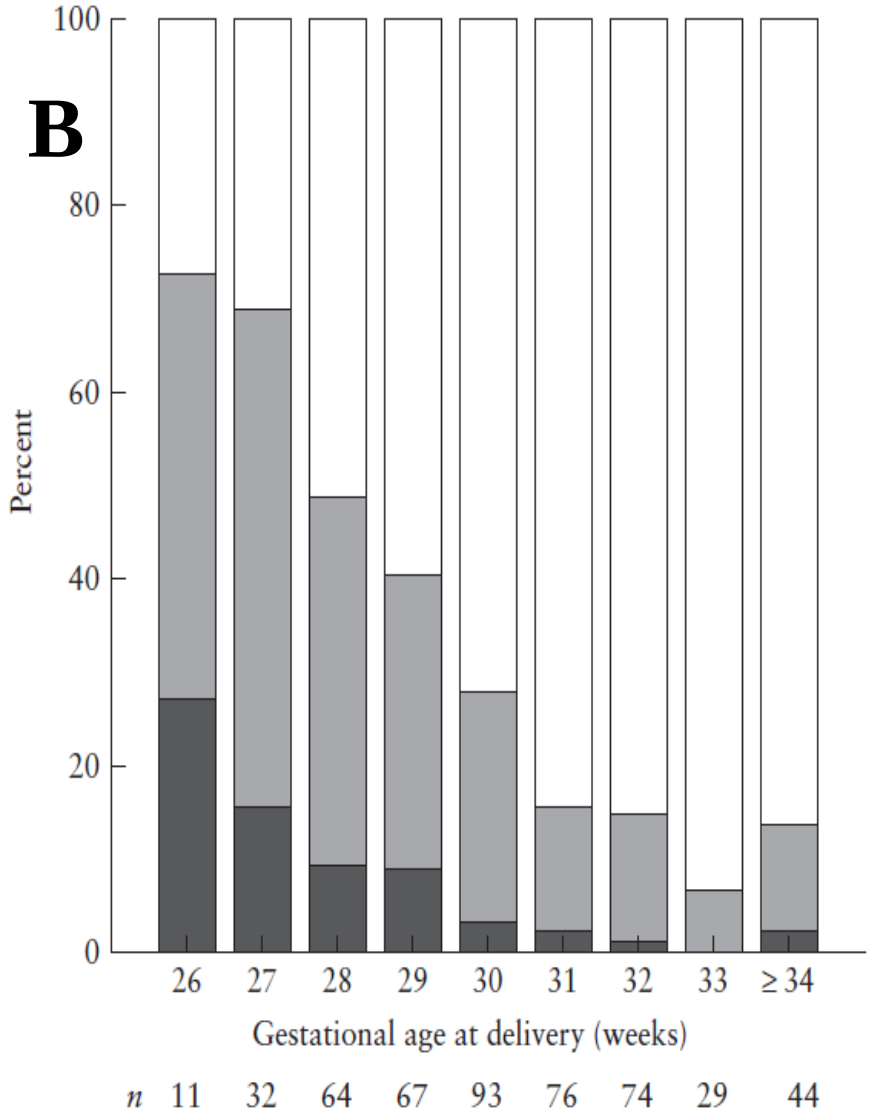



Antepartum deaths 2.4%
(1.3% unexpected)
Neonatal deaths 5.5.%

Lees et al, U O&G Oct 2013

# Outcome according gestational age at inclusion (A) or at delivery (B)



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

Lancet 2015

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

N=503, age at delivery 30.7 wks, birth weight 1019 g

| | | |
|---|---|---|
| • F.death | 12 | 8% |
| • Neonatal/infant death | 29 | |
| • Impairment at 2 y | | 10% |
| • Favourable 2 y outcome | | 82% |

# Cerebral palsy in early IUGR at 2 y

- Torrance et al, UOG 2009, Utrecht,
  1 out of 158

- TRUFFLE, Lees et al, 2016
  6 out of 402

1 %

# 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

# 2 years outcome ( Lees et al, Lancet 2015)

- **Primary outcome**: proportion of infants surviving without neuroimpairment:

| CTG STV | DVp95 | DVnoA |
|---|---|---|
| 77% | 84% | 85% |

- Proportion of survivors without neuroimpairment

| CTG STV | | DVnoA |
|---|---|---|
| 85% (78-90) | P=0.005 | 95% (90-98) |

# 2 years outcome ( Lees et al, Lancet 2015)

- **Primary outcome**: proportion of infants surviving without neuroimpairment:

| CTG STV | DVp95 | DVnoA |
|---|---|---|
| 77% | 84% | 85% |

Interpretation Although the difference in the proportion of infants surviving without neuroimpairment was non-significant at the primary endpoint, timing of delivery based on the study protocol using late changes in the DV waveform might produce an improvement in developmental outcomes at 2 years of age.

# How to monitor early IUGR after TRUFFLE?

- CTG + DV
- DV only, and if so
- Wait for late DV changes?

# However, it is good to realise, that

- In the DV groups twice at many fetuses were delivered because of (safety net) CTG abnormalities than on DV changes
- And that there  was no DV safety net in the CTG arm of the trial

Visser et al, TRUFFLE UOG, 2017

# TRUFFLE, delivery<32 wks, because of CTG or DV abnormality

- N= 217

- CTG abnormality n=165 (decel 79;STV 68, both 18)
- DV abnormality n= 45
- ReDF umb art (>30wks) n= 7

Visser et al, UOG, 2017

# TRUFFLE, delivery<32 wks, because of CTG or DV abnormality

- N= 217

- CTG abnormality n=165 Normal 132 (83%)
- DV abnormality n= 45 Normal 36 (80%)
- ReDF umb art n= 7 Normal 7

Visser et al, UOG

# TRUFFLE, delivery<32 wks, proportion (%) of infants surviving without impairment (Visser et al,UOG 2017)

| Indication for delivery | c- CTG STV | DV p95 | DV no A | All |
|---|---|---|---|---|
| According to randomization arm: | | | | |
| - Specified CTG or DV abnormality | 44/54 (82%) | 26/34 (77%) | 10/11 (91%) | 80/99 (81%) |
| - Safety-net | 15/26 (58%) | 34/37 (92%) | 46/55 (84%) | 95/118 (81%) |
| Other fetal indications* | 7/9 (78%) | 14/15 (93%) | 18/22 (82%) | 39/46 (85%) |
| Maternal | 15/16 (94%) | 11/13 (85%) | 17/18 (94%) | 43/47 (92%) |
| Total, liveborn infants with known outcome | 81/105 (77%) | 85/99 (86%) | 91/106 (86%) | 257/310 (83%) |

# Timing of delivery of the early IUGR fetus (<32 weeks)

**< 26 wks**

- Refrain from intervention?

**>26 wks**

- Abnormal DV PI or reduced c-CTG STV or FHR decelerations. Use a computer analysis to assess FHR variation. Delivery by CS in level-3 center.

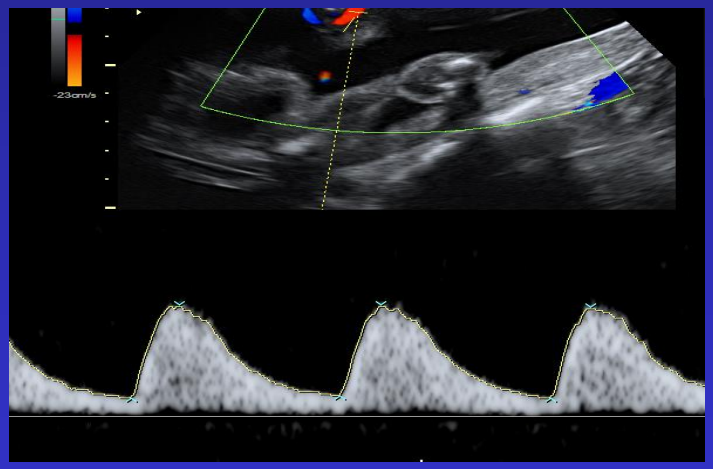
**>30 wks**

- Idem or ReD flow umb art

# Term IUGR/SFD

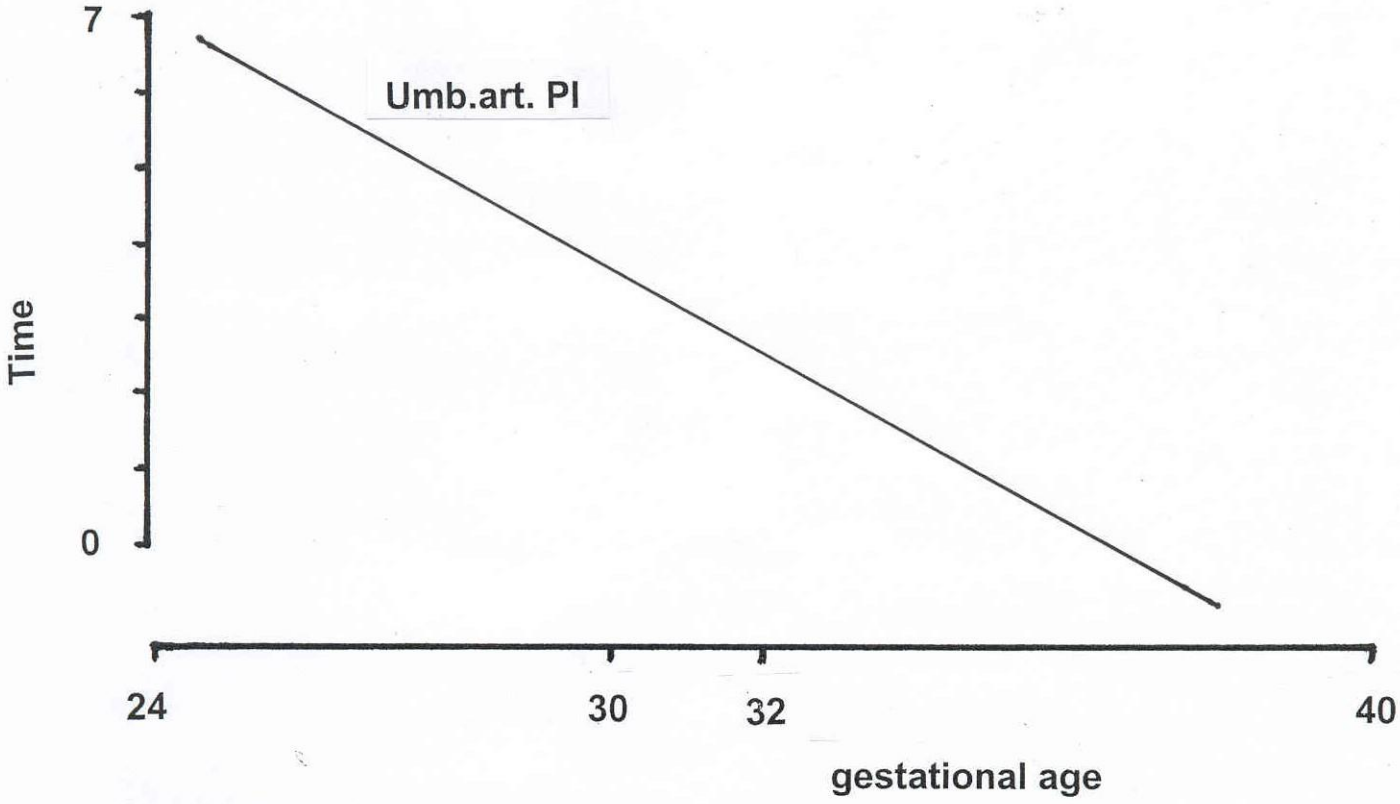
**Many screening and diagnostic tests do not work properly**

(and that holds especially for Doppler umbilical artery)



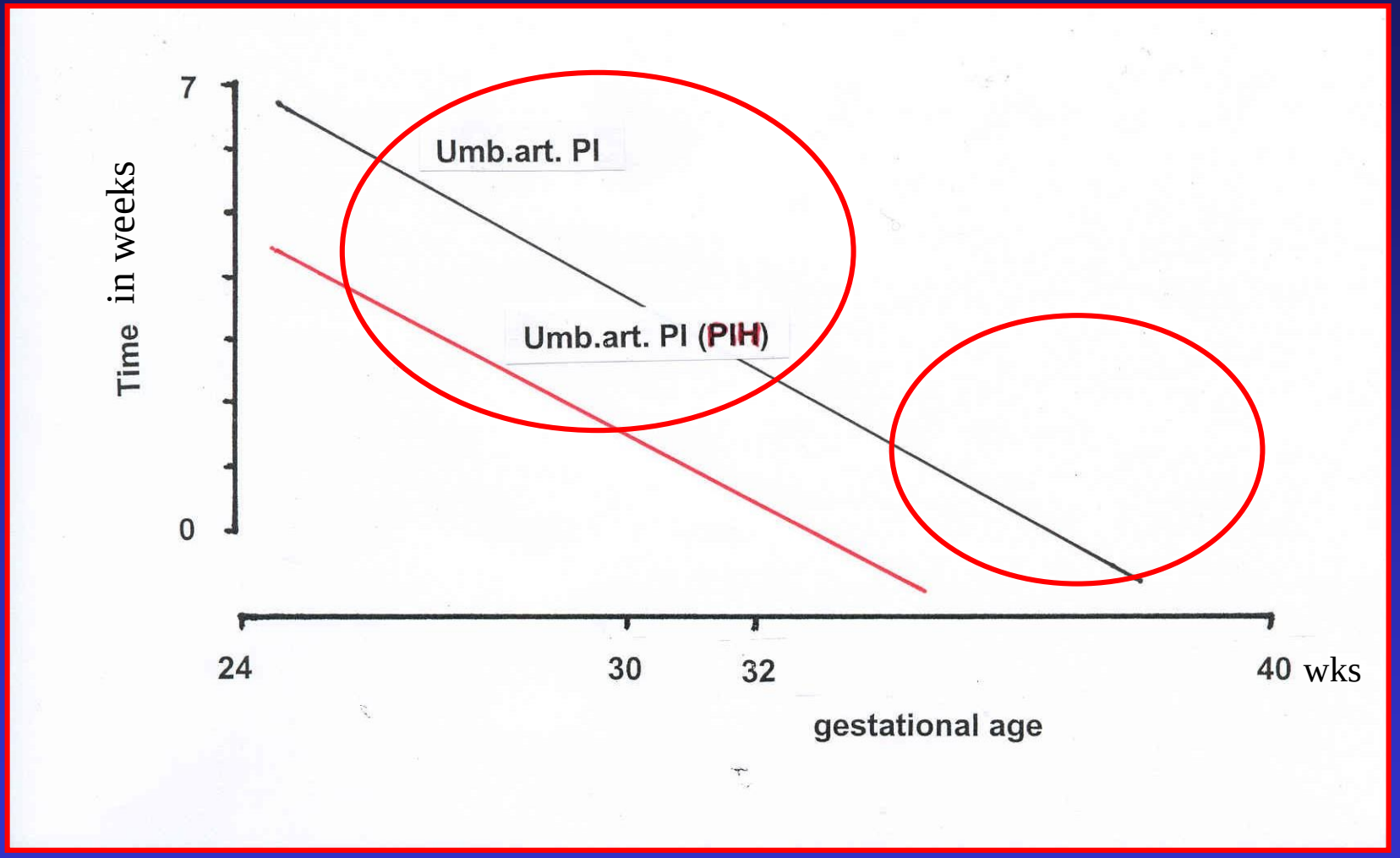
**Moreover, IUGR is not accompanied by maternal hypertensive disease**

# 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.

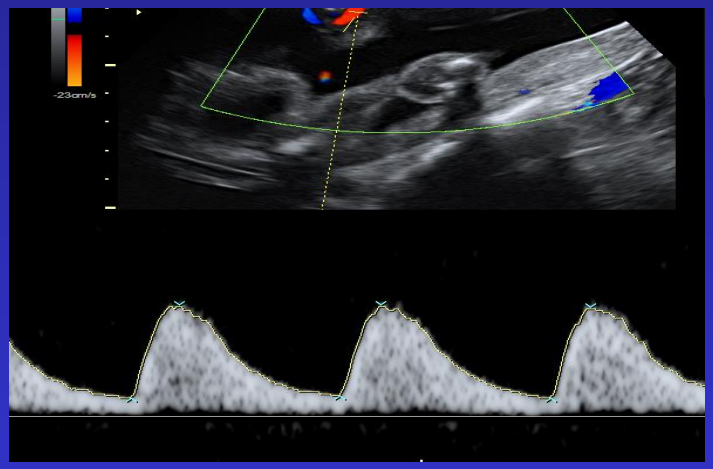
- Early in pregnancy the small fetus can live on ½ a placenta,

- Late in pregnancy the fetus cannot

# Term IUGR/SFD

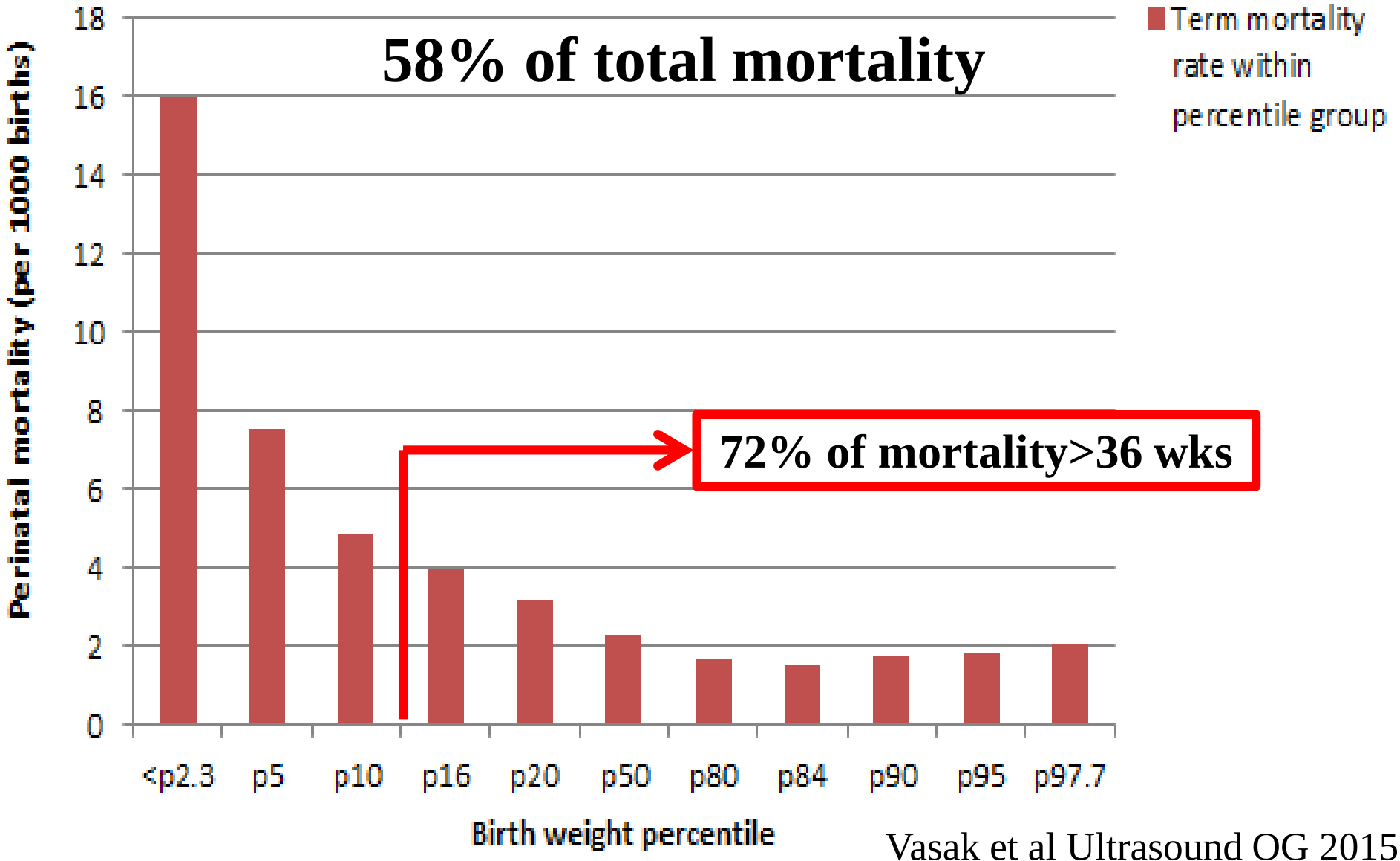
**Many screening and diagnostic tests do not work properly**

(and that holds especially for Doppler umbilical artery)



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

# Perinatal mortality >+36 wks, Nlds 2000-2008



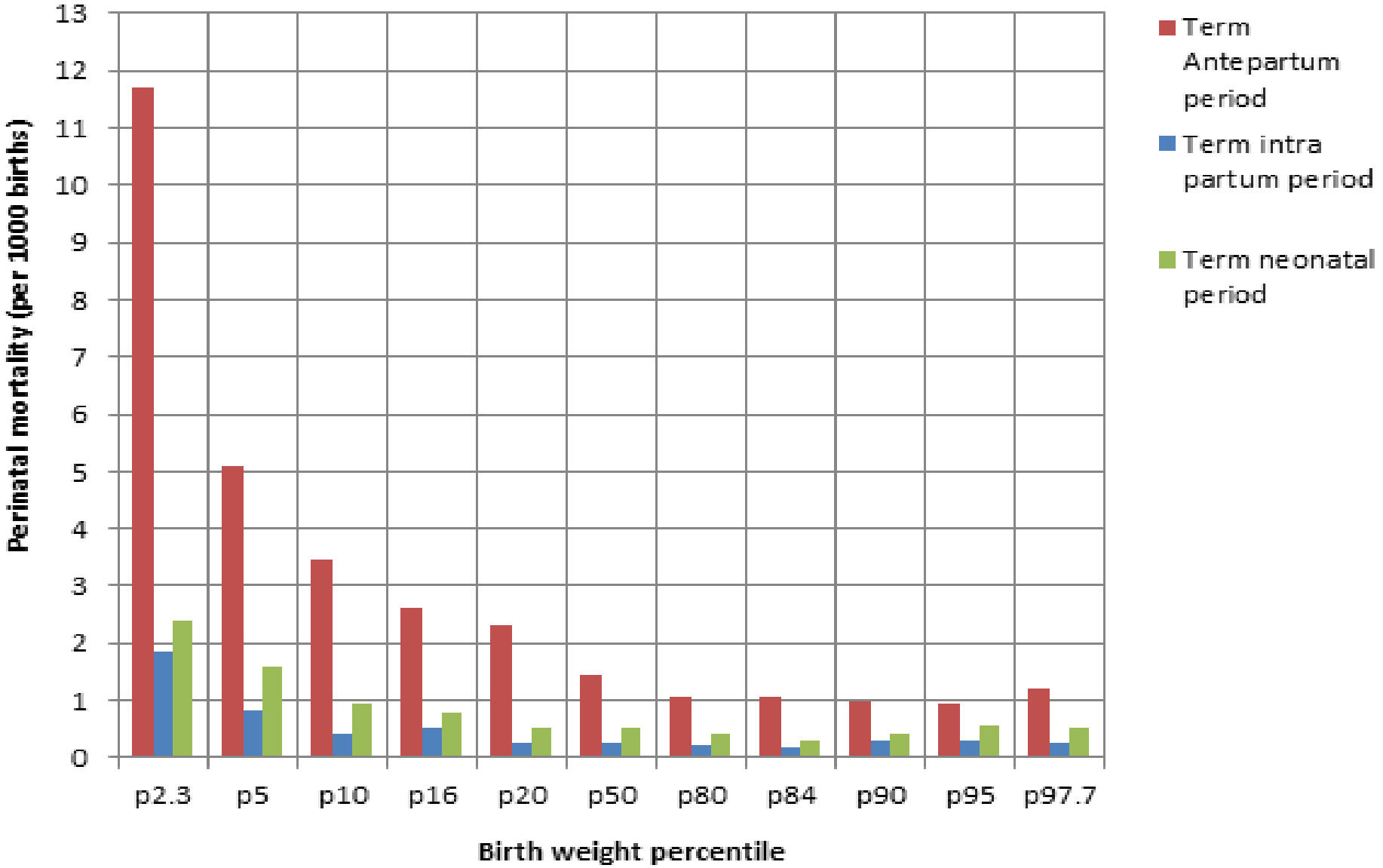

Vasak et al Ultrasound OG 2015

# (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

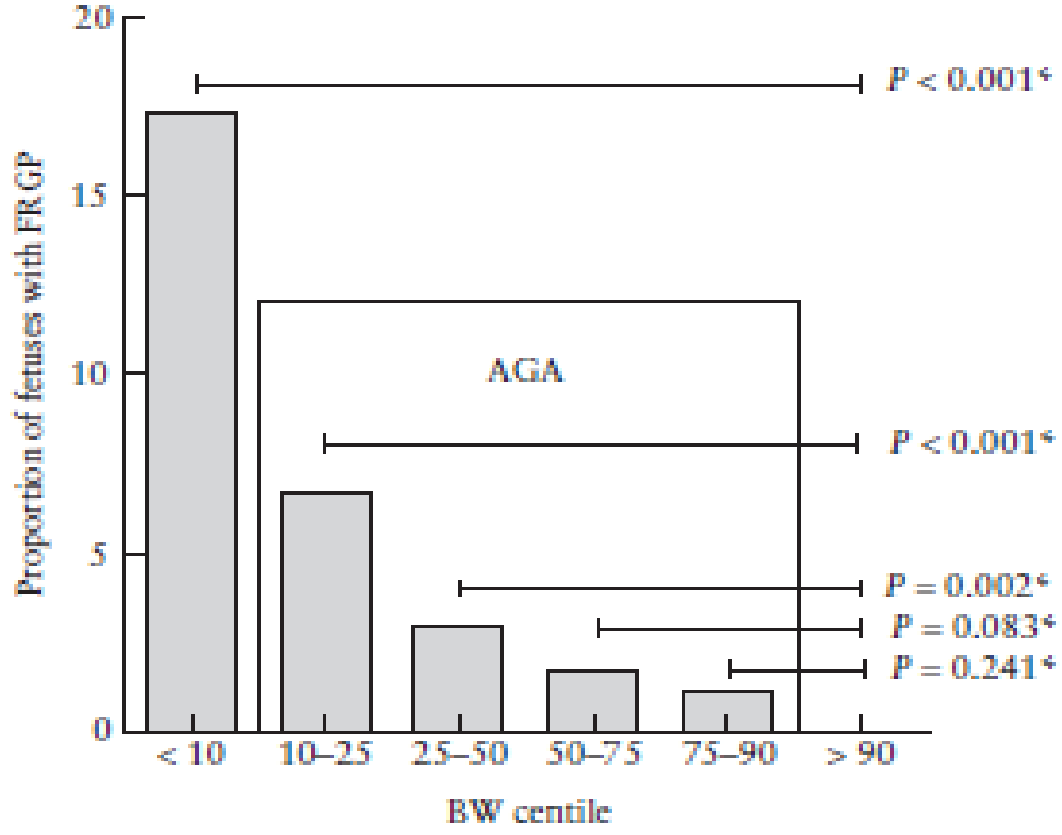



Figure 3 Percentage of term fetuses with failure to reach growth potential (FRGP) according to their birth weight (BW) centile group (i.e. percentage of fetuses presenting a cerebroplacental ratio (CPR) multiple of the median (MoM) value below the established FRGP normality threshold (CPR MoM = 0.6765),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

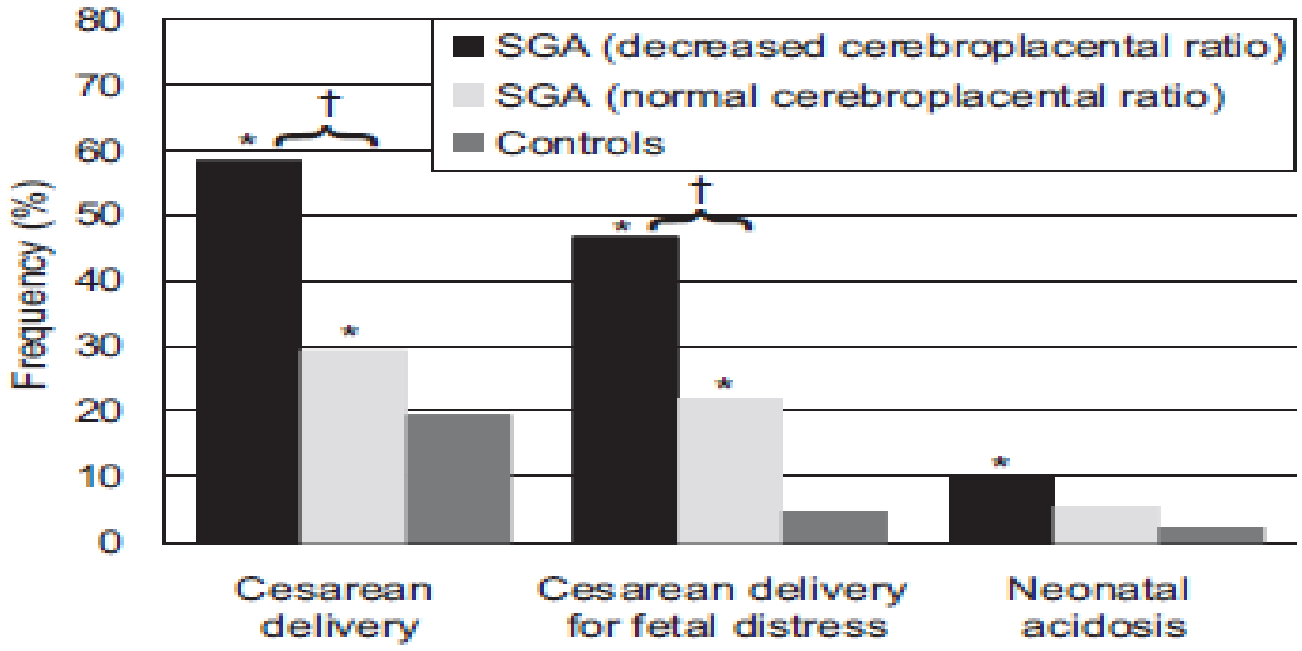



**Fig. 2.** Frequency of intrapartum cesarean delivery, emergency cesarean for nonreassuring fetal status, and neonatal acidosis in controls and small-for-gestational age (SGA) fetuses with and without decreased cerebroplacental ratio. *$P<.05$ with control participants the reference group; †$P<.01$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



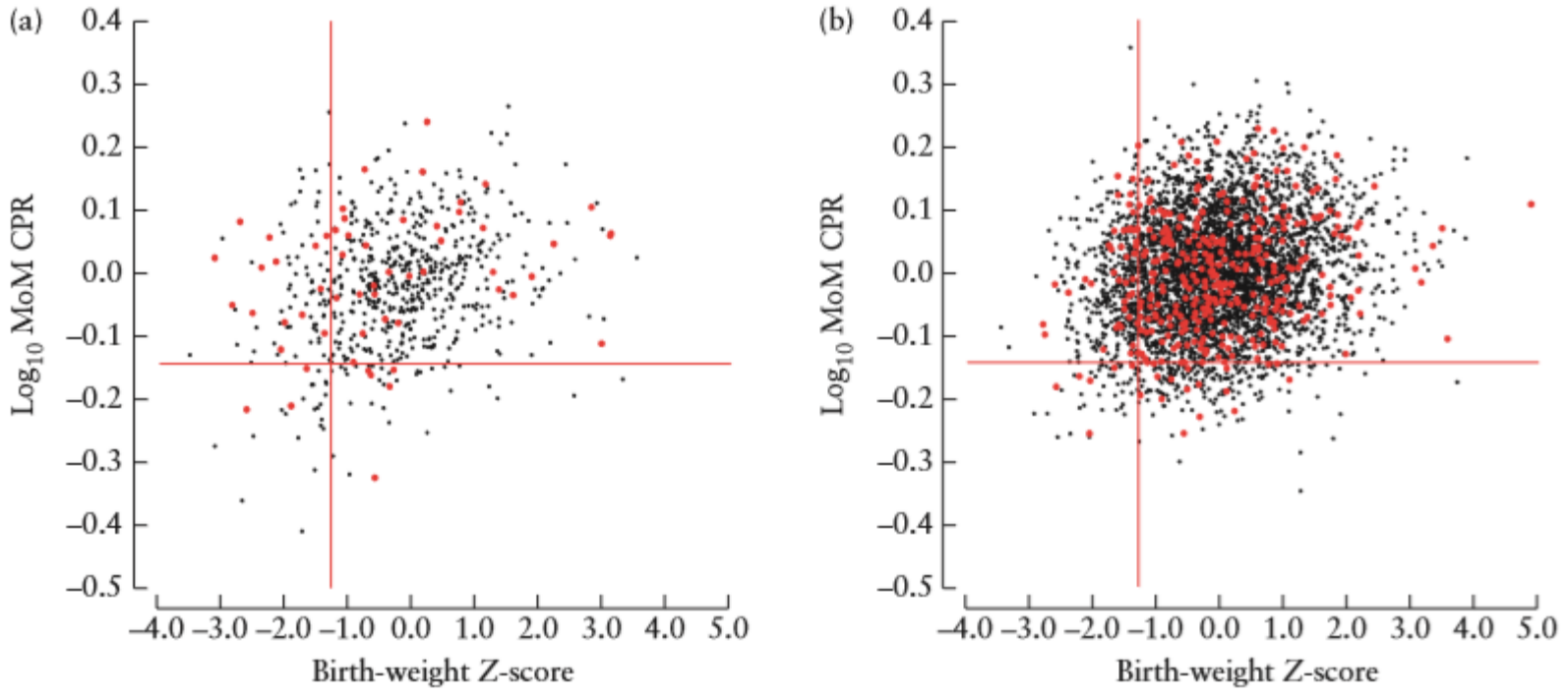



**Figure 3** Relationship between $log_{10}$ multiples of the median (MoM) cerebroplacental ratio (CPR) and birth-weight Z-score in pregnancies delivering by Cesarean section for fetal distress (●) and those delivering vaginally (●) ≤ 2 weeks (a) or > 2 weeks (b) following assessment. Vertical red line 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, UOG, 2016

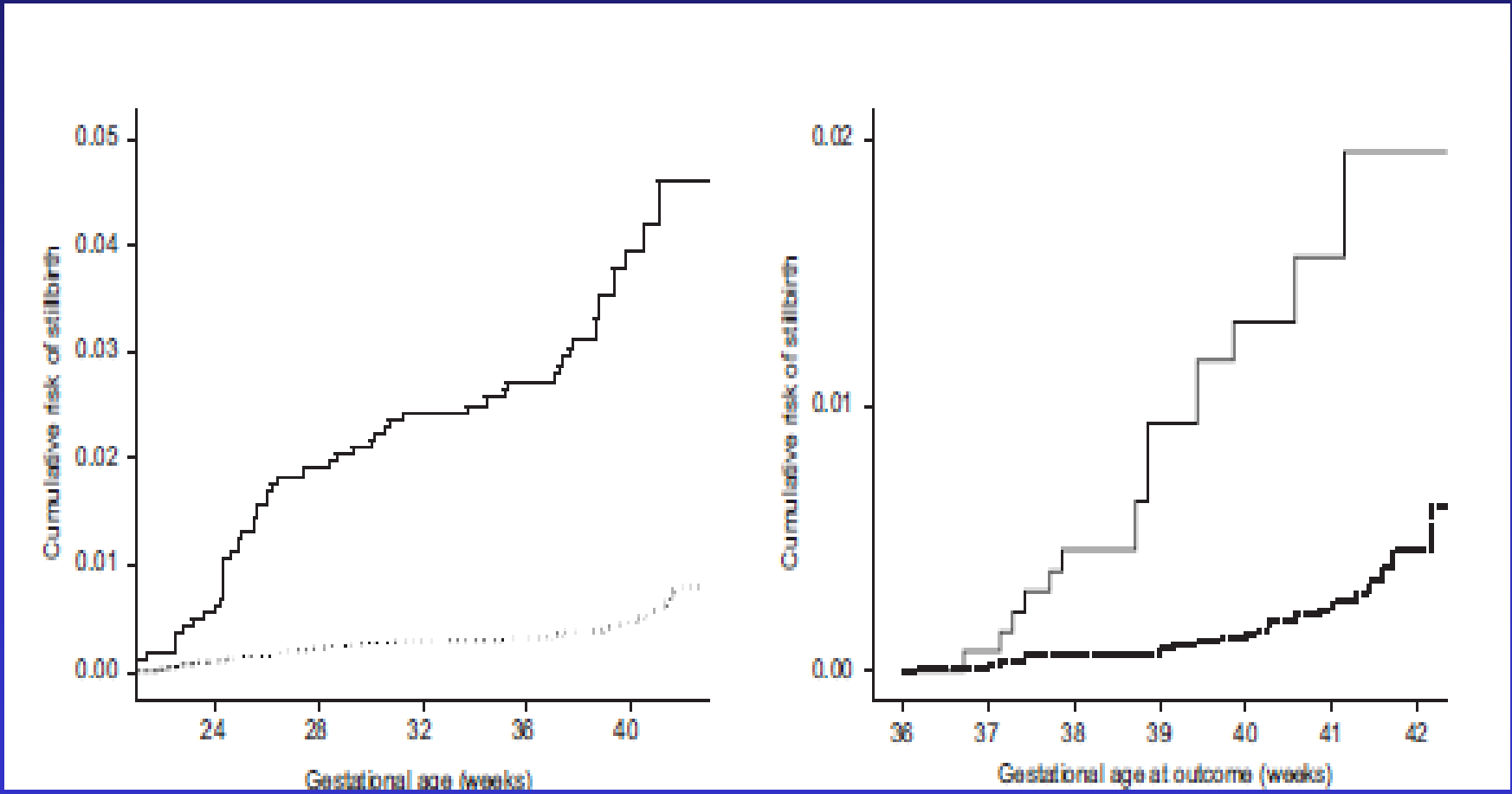
- Low risk cohort of 1000 women
- Measured everything at 37 wks
- Adverse Outcome: 35 in AGA, 5 in SGA & 6 in FGR

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

# 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**

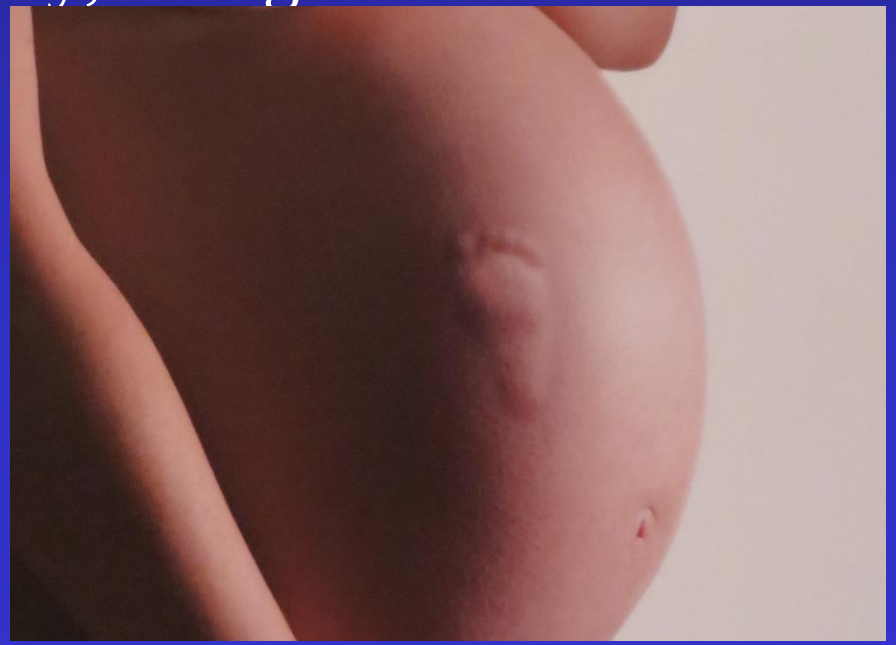
# In this context, it is good to know, that…

- 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

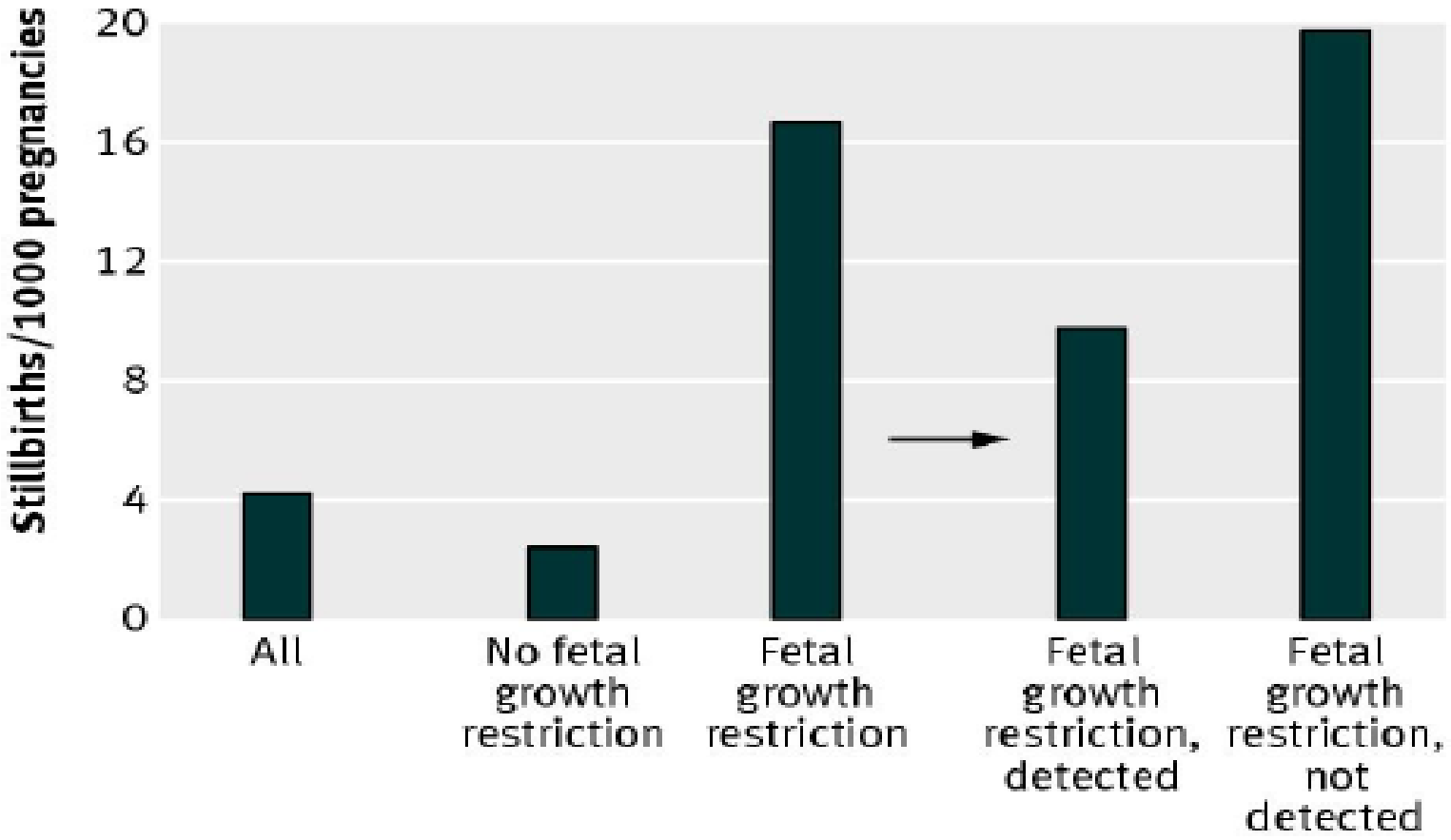
# Structured information on fetal movements at 18 wks

- 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

# 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% |

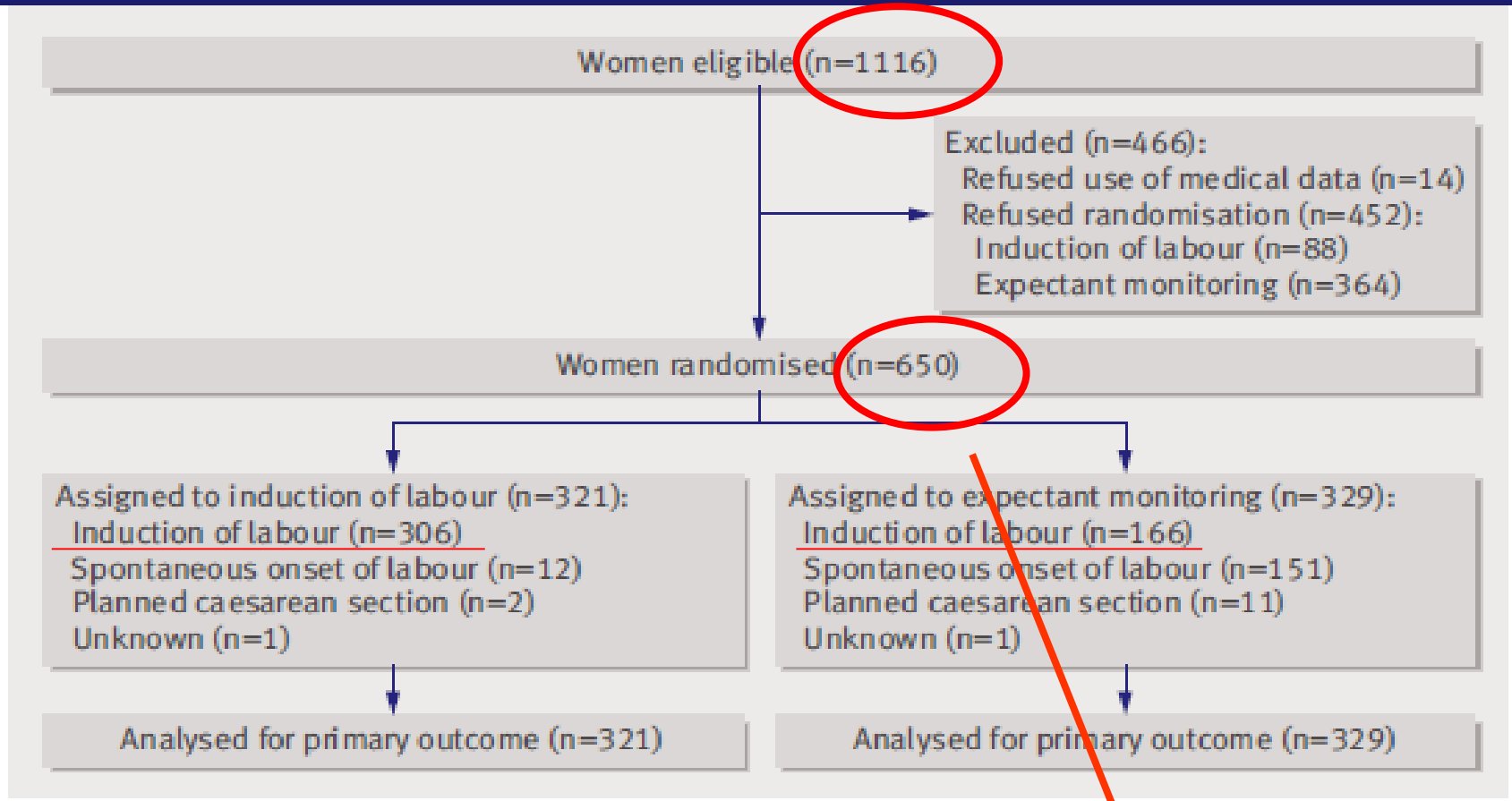
- Screening at 30-34 wks, using mat factors, EFW, UtA PI, MAP, PlGF

  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

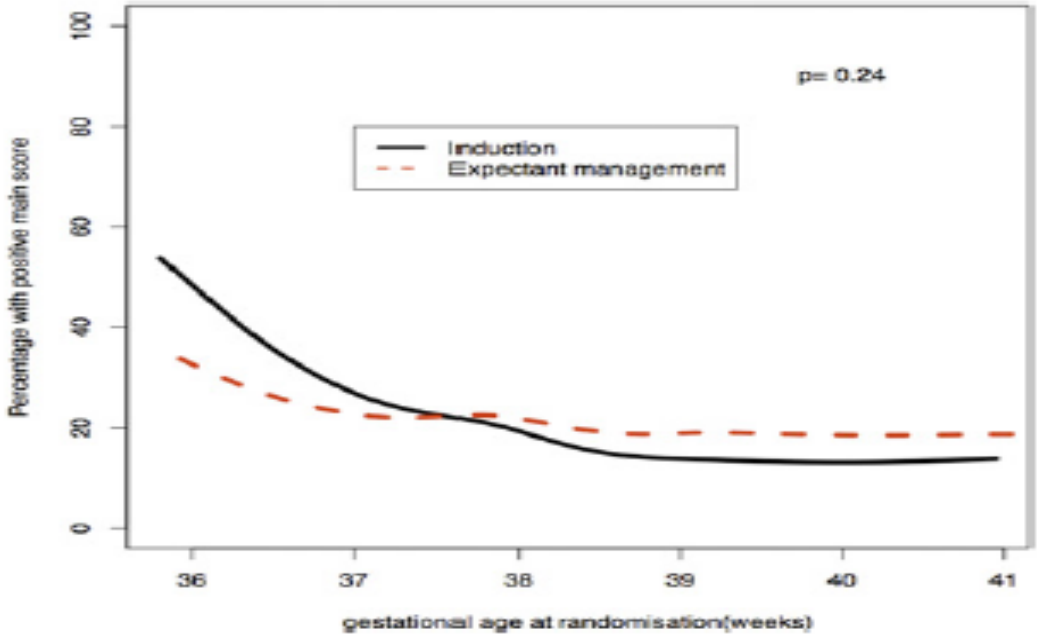
# DIGITAT study

| | 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

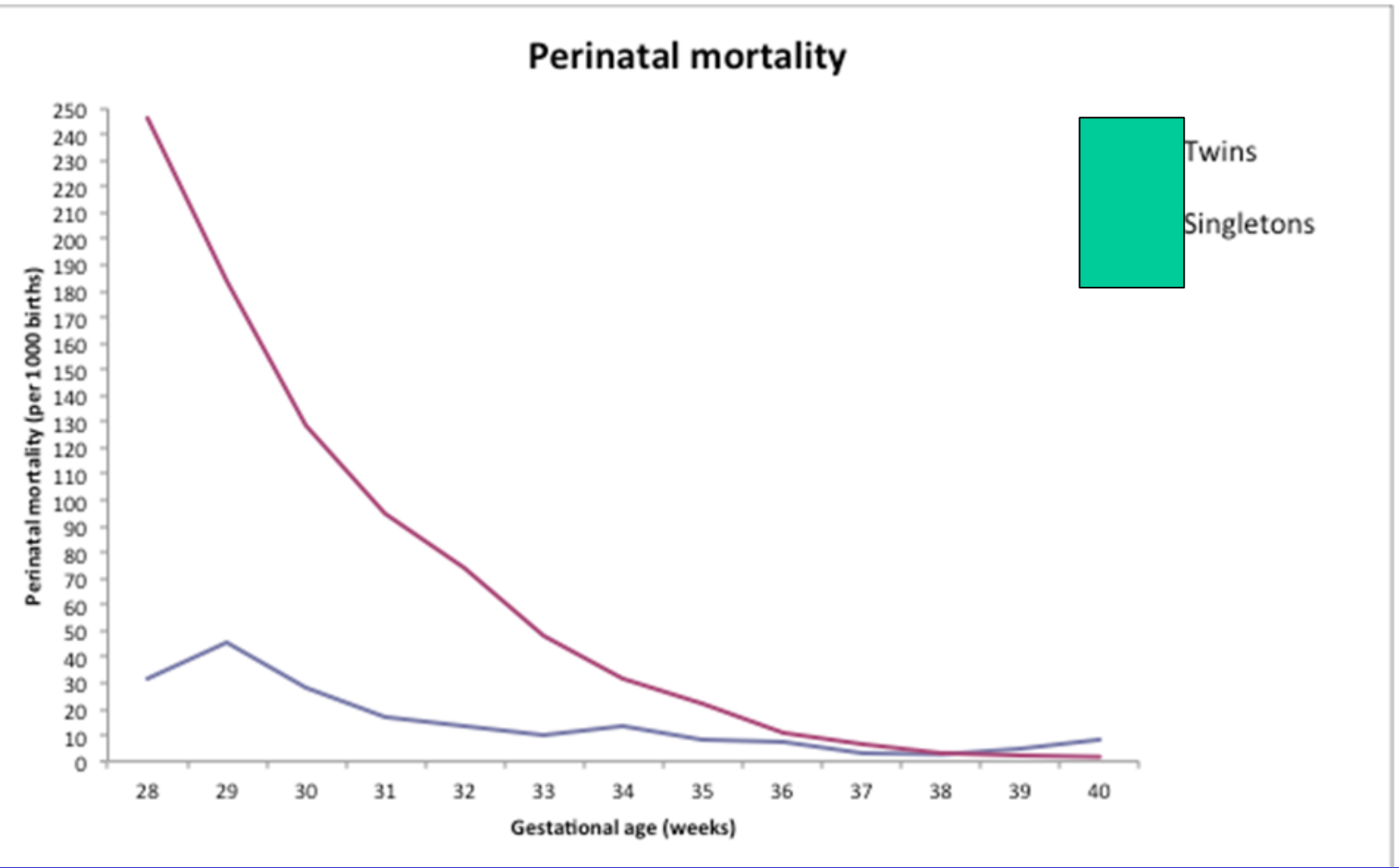
- < 26 wks — Refrain from intervention
- 26-30 wks — Abn DV and/or STV/decelerations
- 30-32 wks — same or reversed EDV umb a
- 32-34 wks — same or absent EDV umb a
- 34-37 wks — same or abn umb a PI
- >37 wks — same or EFW<3rd c,CPR>95th c
- >38+ wks — same or EFW< 10th centile

See also Figueras & Gratacos, 2014

# So,……

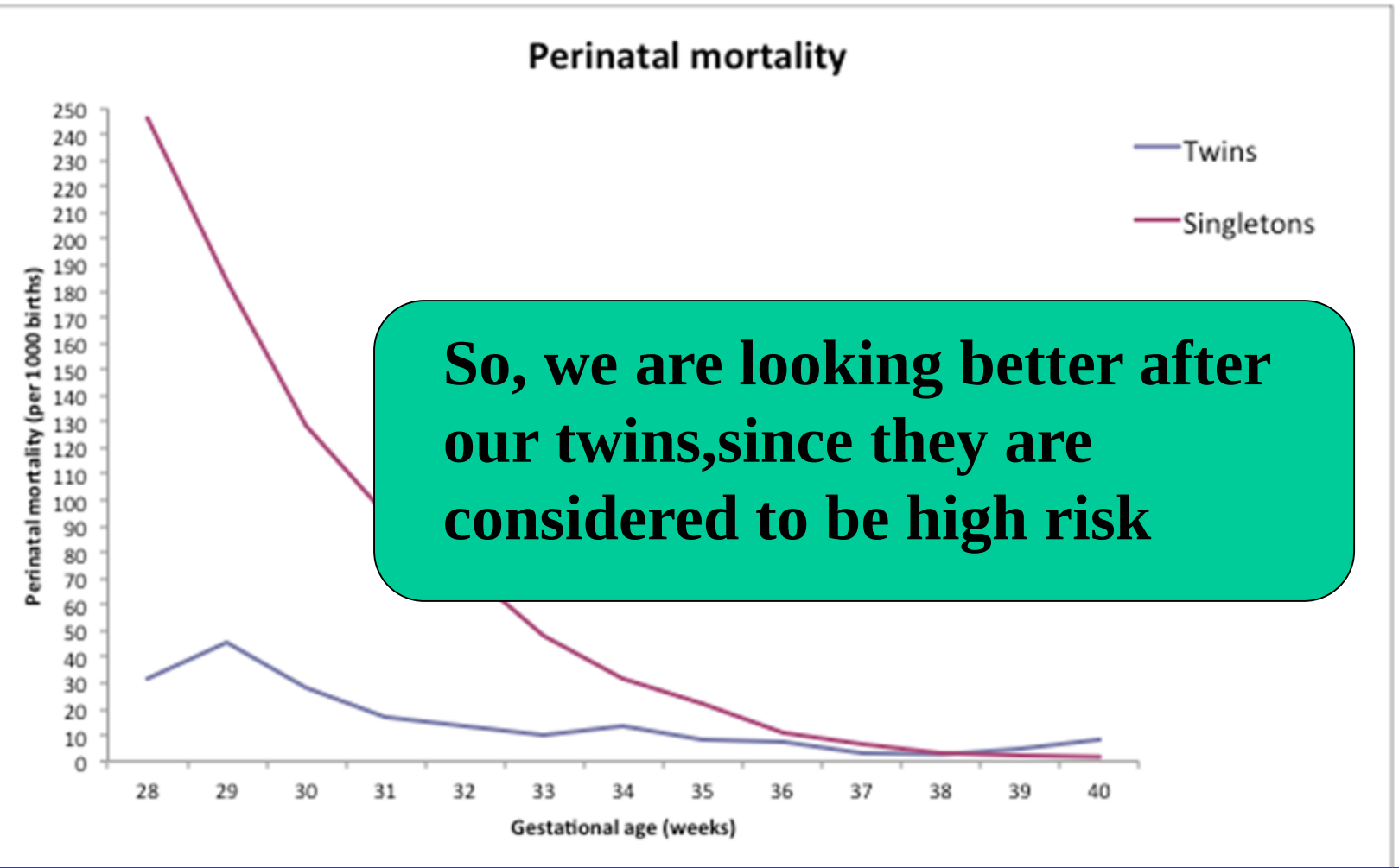
- These are exciting times for all those studying late IUGR
- Diagnosis of SGA is insufficient
- Diagnosis of true (late) IUGR remains difficult
- Assessment may include:
- - monitoring trends in fetal growth
  - Ut artery
  - CP ratio
- What will be the timing of the scan(s)?
- Finally, be aware of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

# Perinatal mortality singletons vs twins




Vasak et al, AJOG 2017

# Perinatal mortality singletons vs twins




**So, we are looking better after our twins,since they are considered to be high risk**

Vasak et al, AJOG 2017

“ 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**