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Preventing Term Stillbirth: Importance of Fetal Weight and Doppler

Conflict of interests: none

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Beginning and end

Early pregnancy screening

- How the current screening system causes harm
- Implementation of better screening strategies

Management at term

- How we assess fetal growth
- Clinical importance of fetal weight/growth
- Does Doppler assessment have a role to play?

Current risk assessment

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Risk factors for pre-eclampsia

Moderate

- First pregnancy
- Age ≥40 years
- Pregnancy interval >10 years
- Body mass index ≥35 kg/m^2 at first visit
- Family history of pre-eclampsia
- Multi-fetal pregnancy

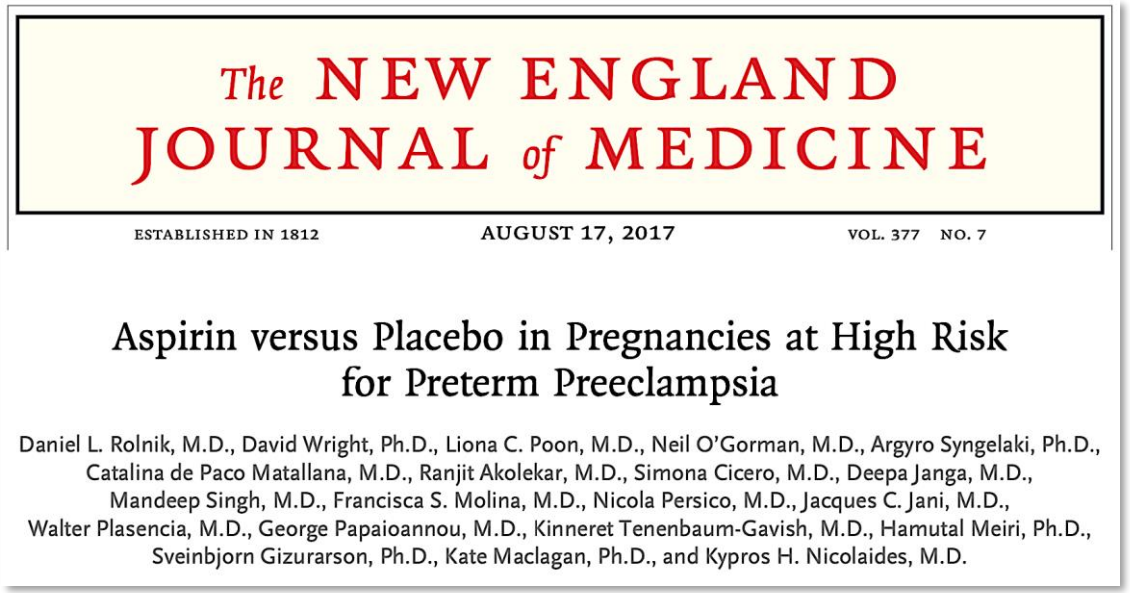
High

- Hypertensive disease during previous pregnancy
- Chronic kidney disease
- Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- Type 1 or type 2 diabetes
- Chronic hypertension

- ❑ Sensitivity 40%, FPR 18%
  - Risk factors not equivalent
  - Thresholds for continuous variables
  - Interaction of risk factors ignored
- ❑ Deprivation/ethnicity excluded
- ❑ <u>No numerical risk provided</u>

Screening for preeclampsia

- **Multicenter, double-blind, placebo-controlled trial**
- **1776 women with singleton pregnancies at high risk for preterm PE**

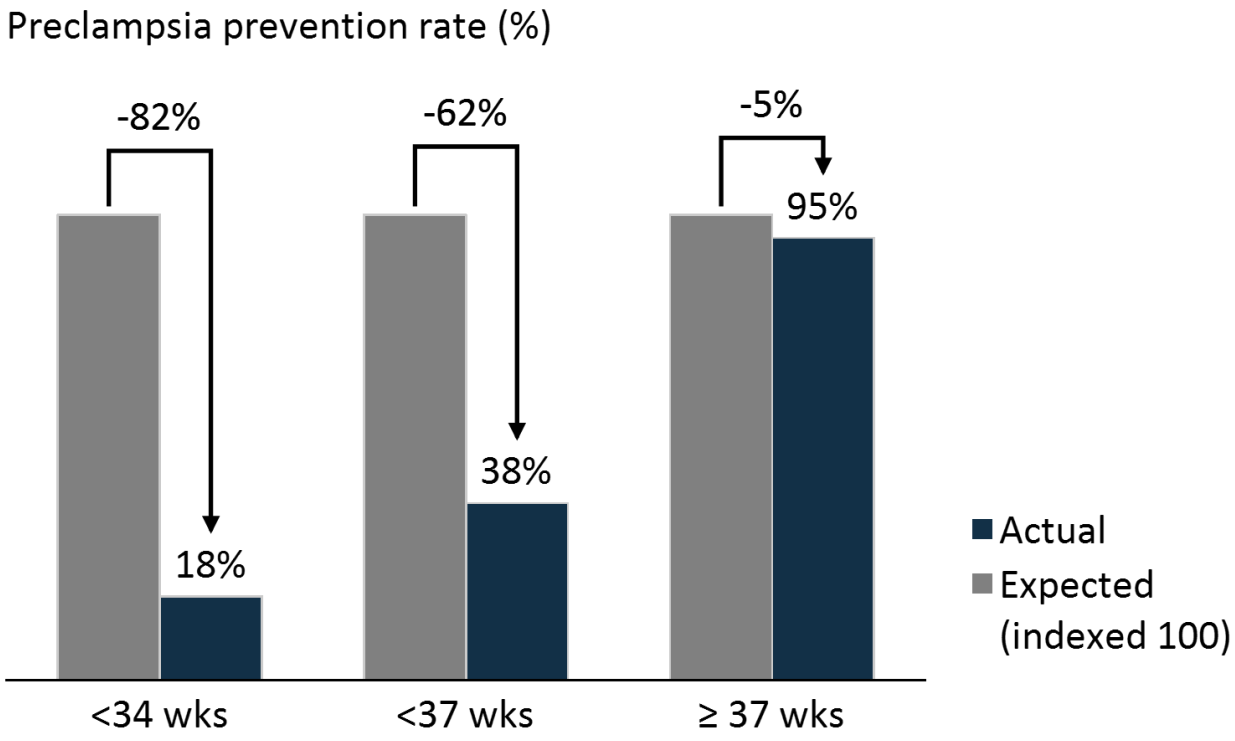


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2017 VOL. 377 NO. 7

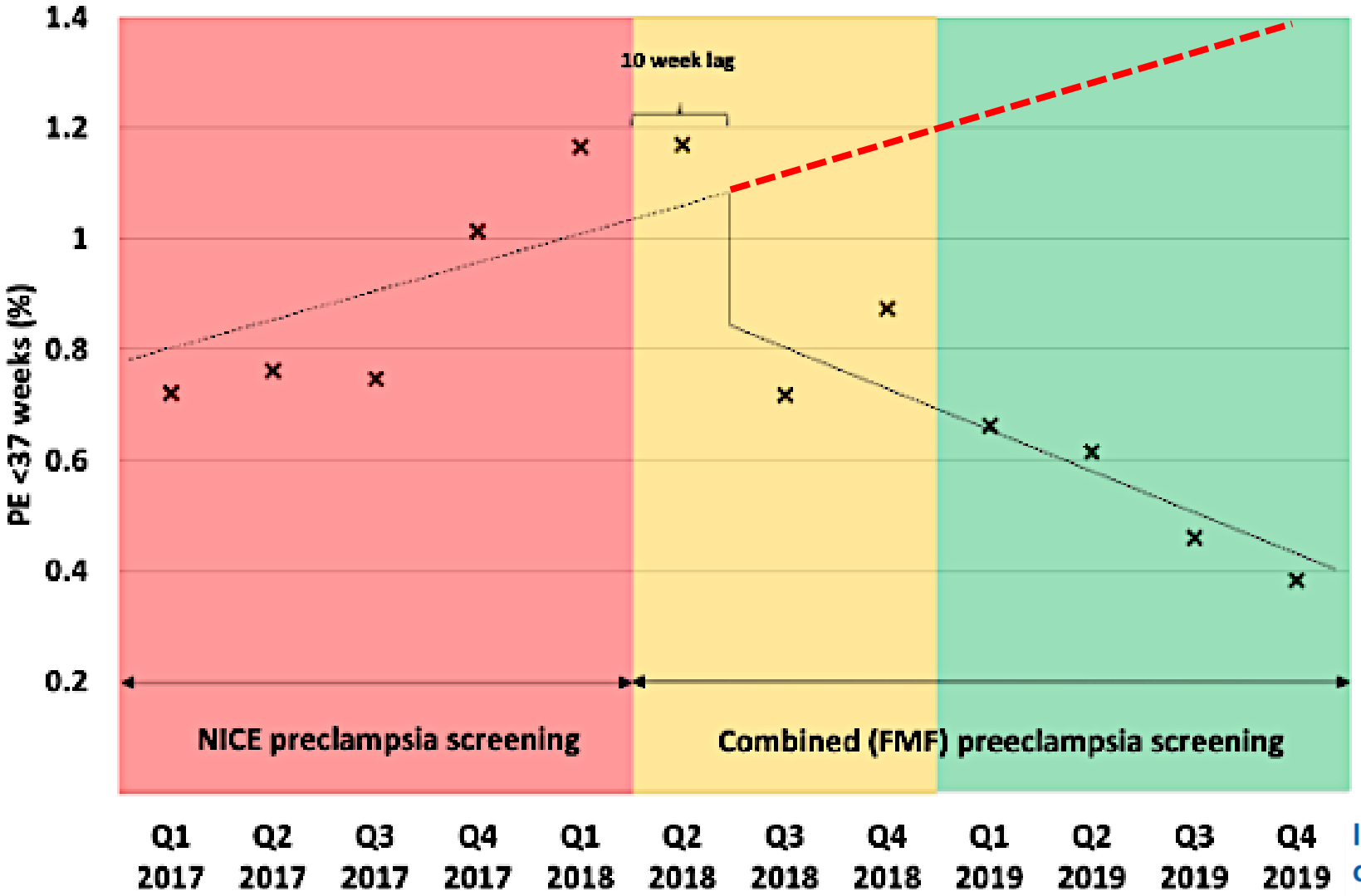
Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Daniel L. Rolnik, M.D., David Wright, Ph.D., Liona C. Poon, M.D., Neil O'Gorman, M.D., Argyro Syngelaki, Ph.D., Catalina de Paco Matallana, M.D., Ranjit Akolekar, M.D., Simona Cicero, M.D., Deepa Janga, M.D., Mandeep Singh, M.D., Francisca S. Molina, M.D., Nicola Persico, M.D., Jacques C. Jani, M.D., Walter Plasencia, M.D., George Papaioannou, M.D., Kinneret Tenenbaum-Gavish, M.D., Hamutal Meiri, Ph.D., Sveinbjorn Gizurarson, Ph.D., Kate Maclagan, Ph.D., and Kypros H. Nicolaides, M.D.



Rolnik D.L., et al., NEJM. 2017

Effectiveness of FMF screening



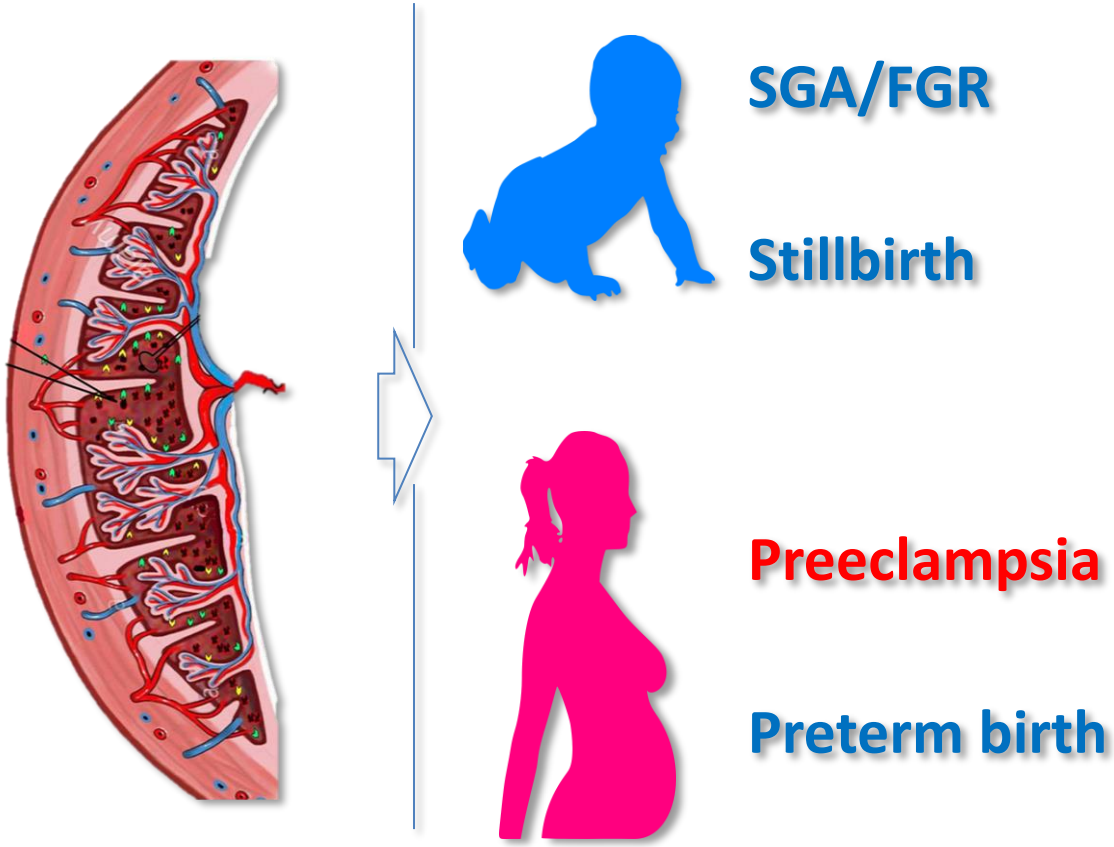
80% relative effect reduction for preterm pre-eclampsia

x4 in aspirin compliance (from 29% to 99%)

Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study

GP Guy,[a,b] K Leslie,[a,c] D Diaz Gomez,[a] K Forenc,[a] E Buck,[a] A Khalil,[a,b] B Thilaganathan[a,b,d]

Placental dysfunction



Adverse pregnancy outcomes in women at increased risk of preterm pre-eclampsia on first-trimester combined screening

Monica Minopoli[1,2] | Laure Noël[3] | Anna Meroni[1,4] | Margaret Mascherpa[1,5] | Alex Frick[1] | Basky Thilaganathan[1,6]

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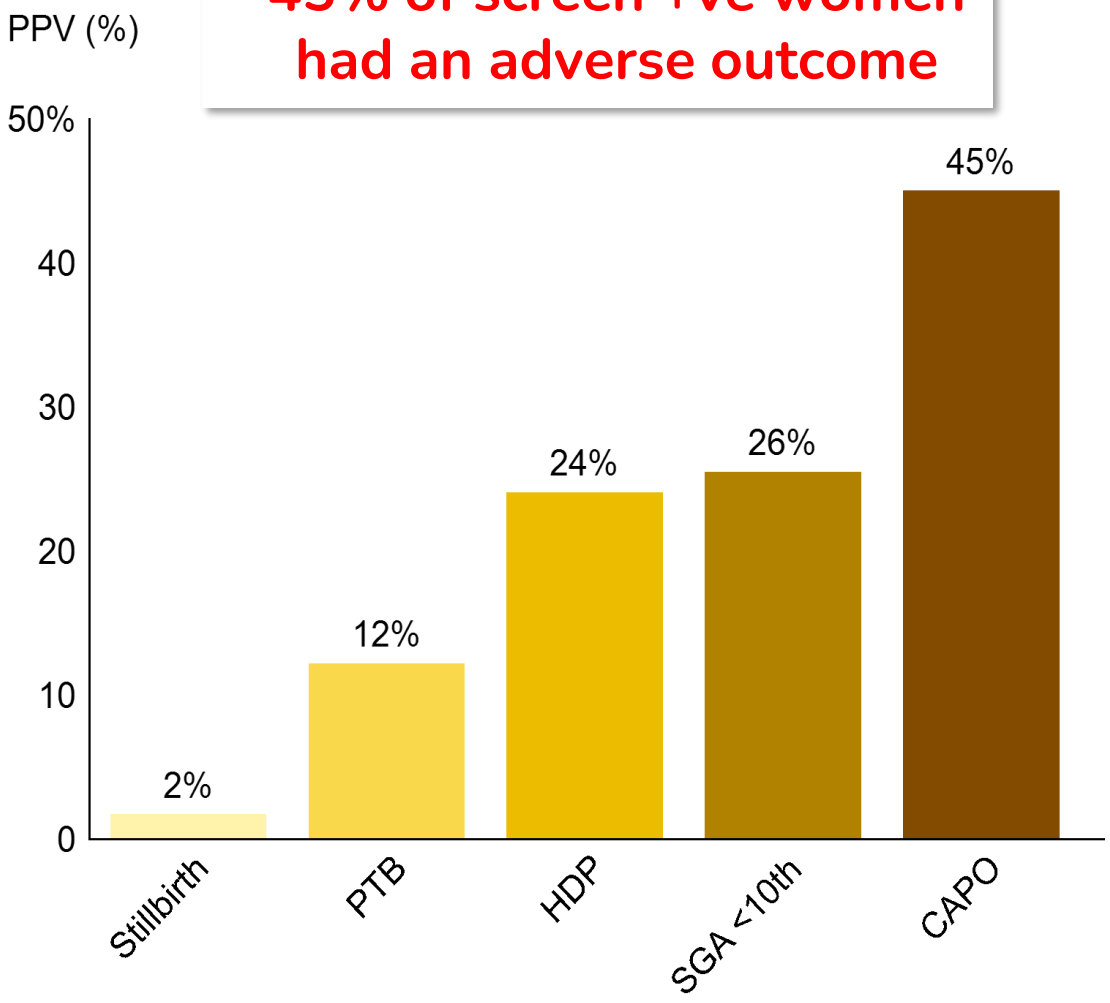
45% of screen +ve women had an adverse outcome



Care pathway

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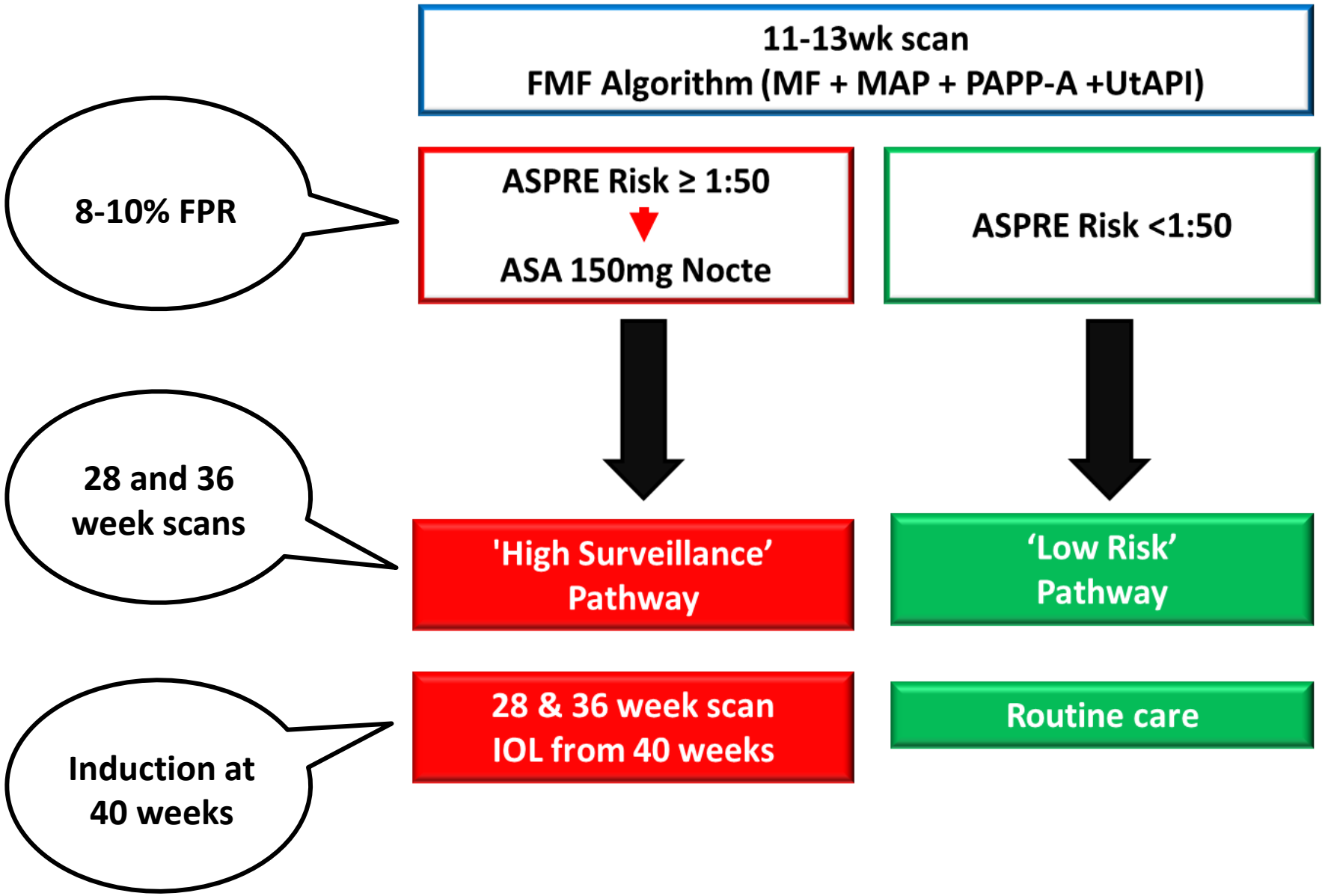
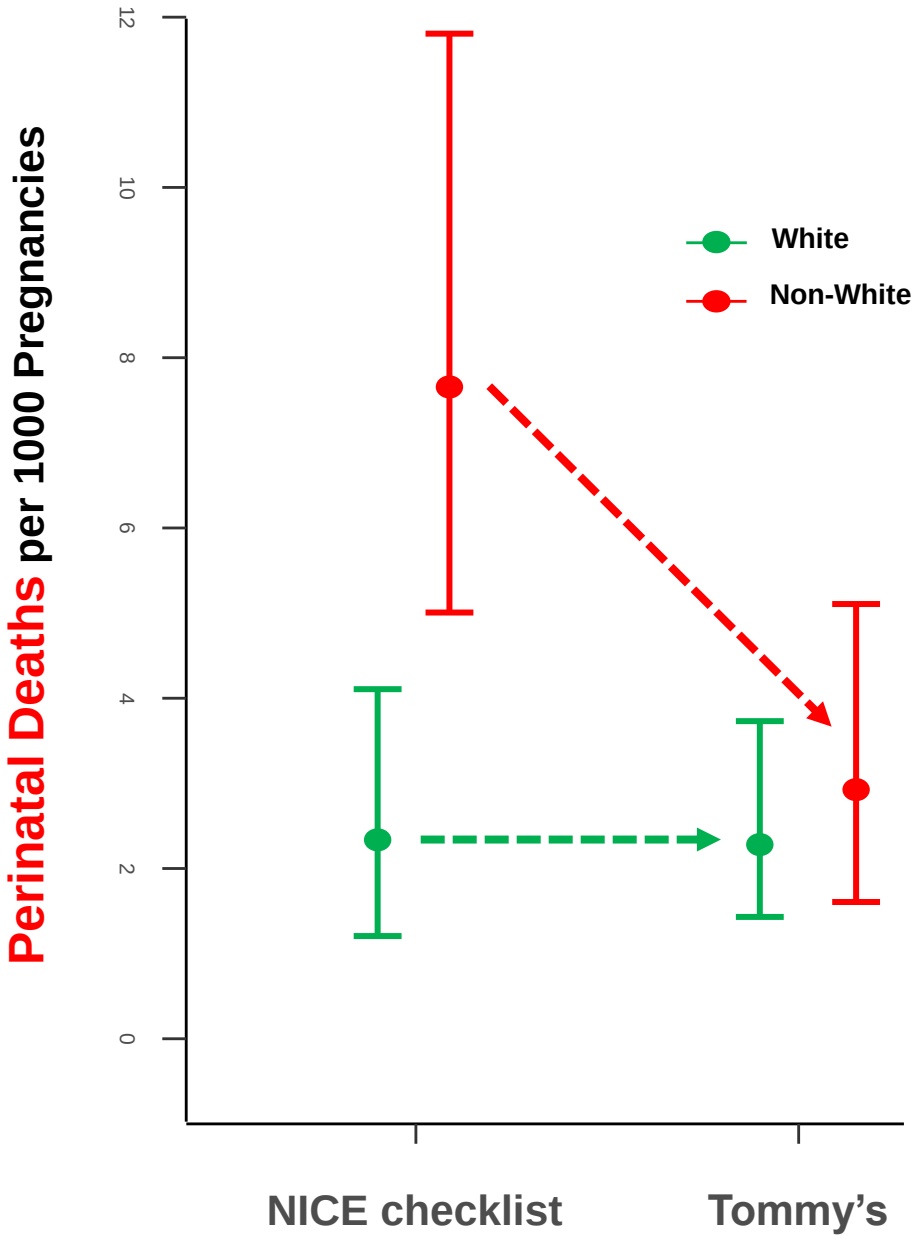


Pregnancy outcomes



Reduction in adverse outcomes

- Improved SGA detection… ↑40%
- Perinatal death (overall)… ↓37%
- Perinatal death (FGR/PE)… ↓72%
- Ethnic health disparity reduced

Effect of routine first-trimester combined screening for pre-eclampsia on small-for-gestational-age birth: secondary interrupted time series analysis

G. P. GUY[1,2], K. LESLIE[1,3], D. DIAZ GOMEZ[1], K. FORENC[1], E. BUCK[1], A. BHIDE[1,2] and B. THILAGANATHAN[1,2,4]

Reducing health inequality in Black, Asian and other minority ethnic pregnant women: impact of first trimester combined screening for placental dysfunction on perinatal mortality

Becky Liu[1,2] | Usaama Nadeem[2] | Alexander Frick[1,2] | Morakinyo Alakaloko[1] | Amar Bhide[1,2] | Basky Thilaganathan[1,2,3]

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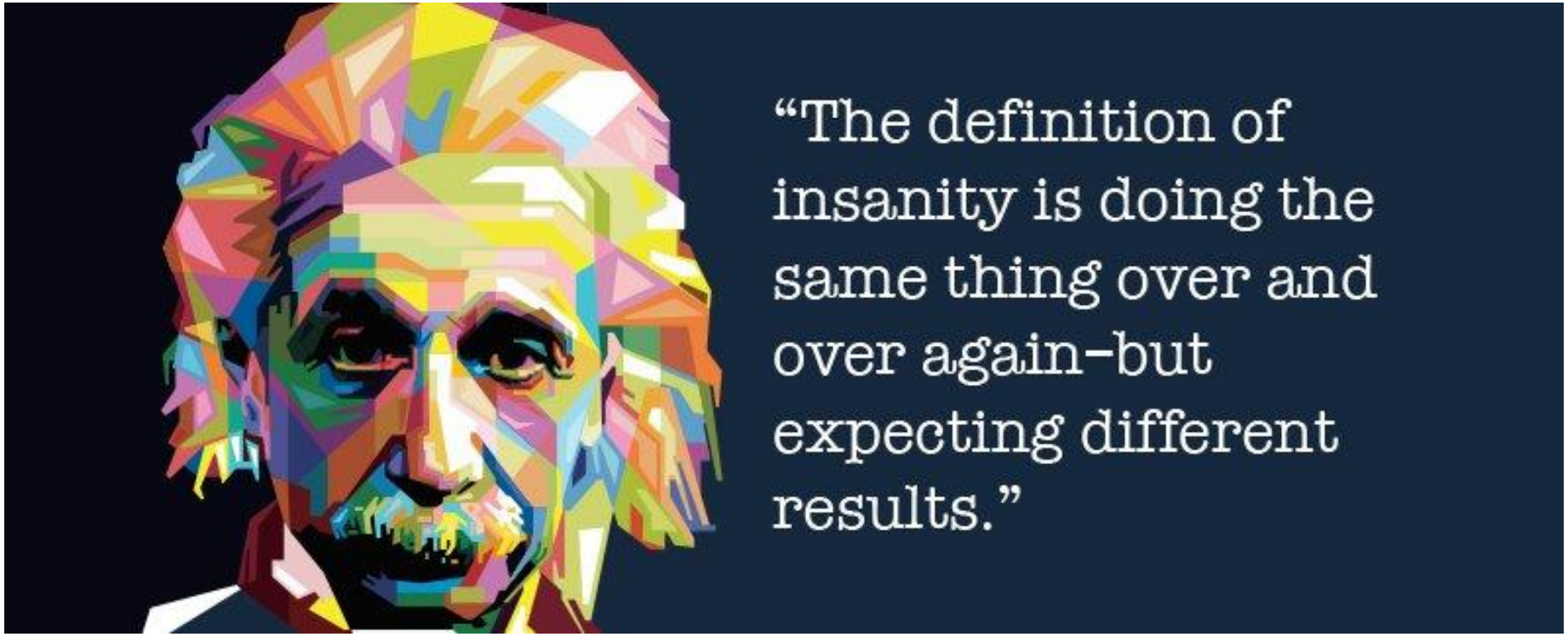
The continued use of maternal risk-factor based screening for placental disorders in routine healthcare settings MUST be re-evaluated



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Beginning and end

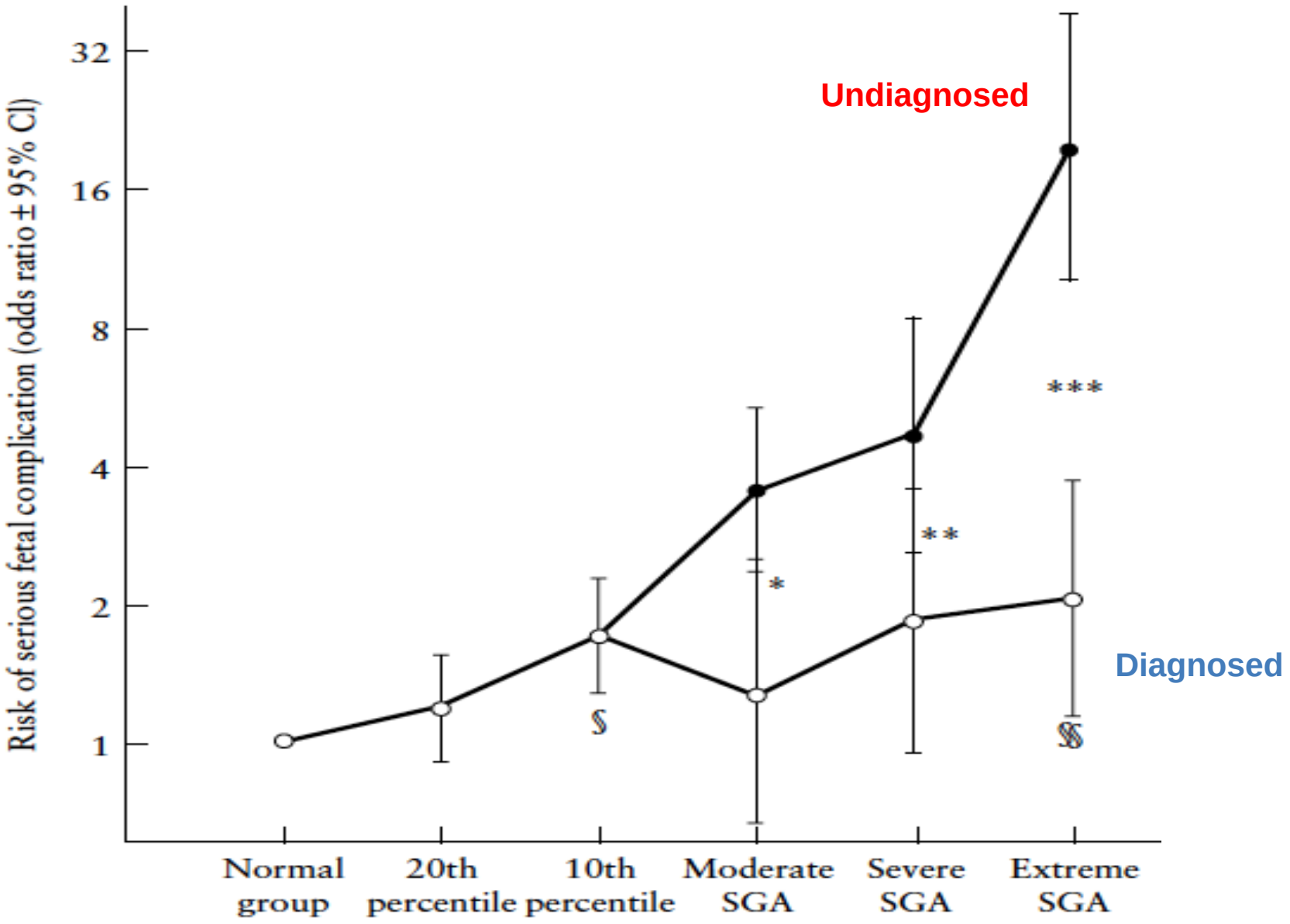
Early pregnancy screening

- How the current screening system causes harm
- Implementation of better screening strategies

Management at term

- How we assess fetal growth
- Clinical importance of fetal weight/growth
- Does Doppler assessment have a role to play?

Birth weight and mortality



Lindqvist PG *et al.* UOG 2005

WHEN IS THE BEST TIME TO SCAN IN THE 3RD TRIMESTER?

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When to perform the scan?

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Ultrasound screening for fetal growth restriction at 36 *vs* 32 weeks' gestation: a randomized trial (ROUTE)

E. ROMA*, A. ARNAU†, R. BERDALA*, C. BERGOS*, J. MONTESINOS† and F. FIGUERAS‡

RCT - 32 vs 36wk scan

2856 women

Outcome: SGA detection

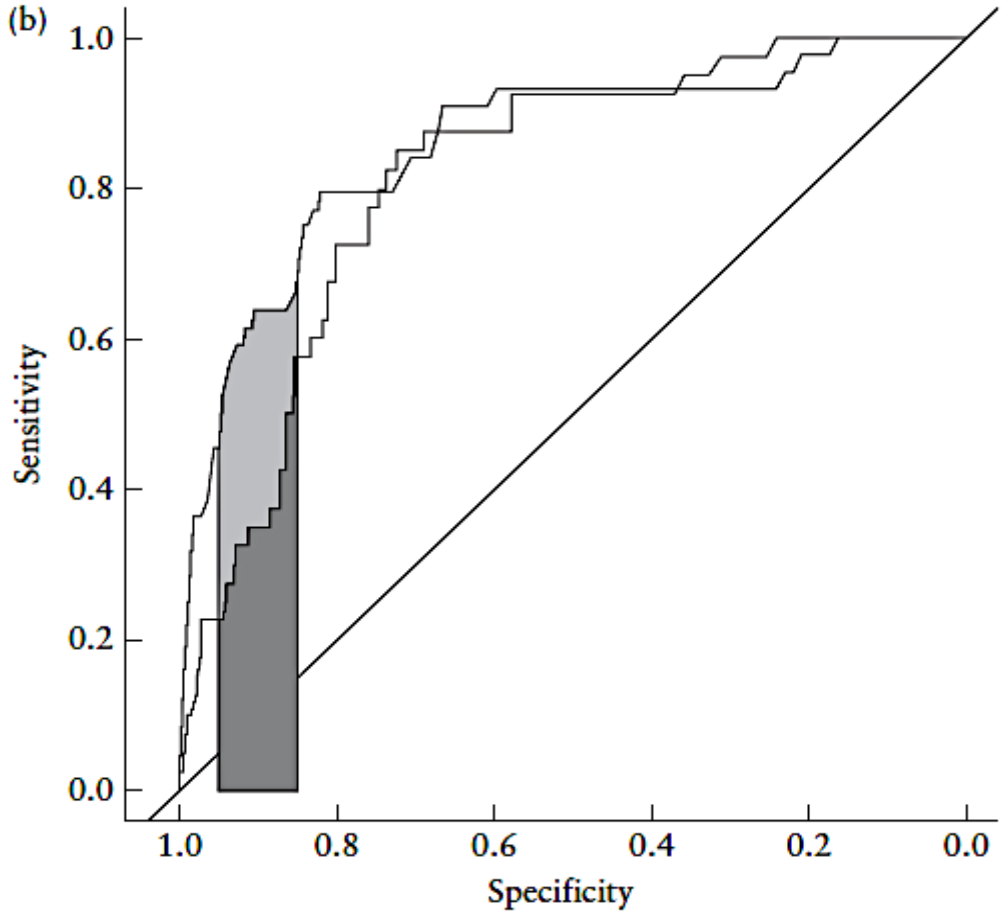

Figure 2 Areas under the receiver–operating characteristics curve for ultrasound examinations at 32 (■) and 36 (□) weeks' gestation for prediction of fetal growth restriction (a) and severe fetal growth restriction (b). Shaded area indicates a 5–15% range of false-positive rate.

WHAT IS THE BEST WAY TO ESTIMATE FETAL SIZE?

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Estimating fetal weight

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Accurate estimation of fetal weight

- Use HC, AC, FL
- Hadlock (1985) or
- Hammami (2018)

Study	All pregnancies				BW < 2500 g	
	MPE (%) (95% CI)	AE ± SD (%)	AE ≤ 10%	ED	AE ≤ 10%	ED
Nzeh (1992)[34]	8.1 (−14.6 to 30.8)	10.4 ± 9.5	60.5	14.1	12.9	25.1
Halaska (2006)[35]	4.7 (−20 to 29.4)	10.0 ± 9	61.8	10.5	19.3	23.3
Ben-Haroush (2008)[19]	2.8 (−13.9 to 19.4)	7.0 ± 5.6	75.6	8.9	54.1	12.9
Siemer (2009)[36] (small)	−11.1 (−35 to 12.8)	14.3 ± 8.2	32.7	16.5	66.6	11.8
Akhtar (2010)[20]	−21.2 (−48.5 to 6.1)	21.7 ± 13.2	19.4	25.4	40.5	28.2
Kehl (2012)[37] (small)	21.9 (−4 to 47.8)	22.2 ± 12.6	19.1	25.6	45.7	16.8
This study	0.4 (−14.8 to 15.6)	6.2 ± 4.7	80.3	7.8	75.4	8.9
HC, AC, FL						
Hadlock (1985)[15]	0.7 (−14.5 to 16)	6.3 ± 4.7	79.9	7.8	72.8	9.1
Weiner (1985)[25] (small)	−8.1 (−23.5 to 7.2)	9.5 ± 6.2	57.0	11.3	57.4	11.1
Ott (1986)[38]	2.1 (−14.3 to 18.6)	6.8 ± 5.3	76.4	8.7	57.1	12.1
Combs (1993)[39]	0.6 (−16.9 to 18.1)	7.0 ± 5.5	74.7	9.0	54.0	12.7
Dudley (1995)[40]	−4.0 (−19.1 to 11.1)	7.1 ± 5	73.7	8.7	75.2	8.7
Scott (1996)[41] (small)	−12.3 (−29.6 to 5)	13.3 ± 7.2	34.7	15.1	77.8	8.3
Schild (2004)[42] (small)	−18.1 (−33.9 to −2.2)	18.3 ± 7.5	14.5	19.8	51.5	11.7
This study	−0.3 (−15.4 to 14.8)	6.2 ± 4.6	80.3	7.7	75.8	8.5
BPD, HC, AC, FL						
Hadlock (1985)[15]	2.7 (−12.8 to 18.1)	6.7 ± 5	77.7	8.3	69.8	9.8
Roberts (1985)[43] (small)	15.3 (−5.9 to 36.5)	15.9 ± 9.9	31.6	18.8	41.6	16.5
Ben-Haroush (2008)[19]	2.8 (−13.8 to 19.4)	6.9 ± 5.6	75.6	8.9	53.8	12.9
Chen (2011)[44]	12.9 (−6 to 31.7)	13.6 ± 8.5	38.1	16.1	26.0	19.5
Chen (2011)[44] (small)	−12.6 (−39.4 to 14.2)	15.7 ± 10.1	33.4	18.6	66.0	11.4
Chen (2011)[44] (large)	35.6 (−27.7 to 98.9)	36.5 ± 31.3	18.4	48.0	0	87.9
Souka (2014)[45]	0.2 (−30.6 to 30.9)	8.5 ± 13.2	73.9	15.7	46.8	30.3
Souka (2014)[45] (large)	4.5 (−40.1 to 49.1)	12.3 ± 19.7	57.4	23.2	30.8	45.1
Souka (2014)[45] (small)	−19.4 (−60 to 21.3)	21.1 ± 19	27.7	28.4	66.9	36.9
This study	0.2 (−14.9 to 15.2)	6.2 ± 4.6	80.4	7.7	75.2	8.6
BPD, HC, AC, FL, GA						
Sabbagha (1989)[46]	−1.3 (−18.7 to 16.1)	7.1 ± 5.5	74.9	9.0	62.8	11.7
Sabbagha (1989)[46] (large)	4.3 (−28.7 to 37.2)	9.4 ± 14.5	71.5	17.3	36.3	34.0
Sabbagha (1989)[46] (small)	−2.8 (−18.8 to 13.3)	6.9 ± 5.1	75.4	8.6	73.2	9.4
This study	0.6 (−15.2 to 16.4)	6.5 ± 4.9	79.0	8.1	76.3	8.9
Two-stage screening						
Hadlock (1985)[15] (HC, AC, FL), Scott (1996)[41] (HC, AC, FL), Ferrero (1994)[18] (AC, FL)	0.2 (−16.1 to 16.5)	6.5 ± 5	77.3	8.3	70.5	9.4

Ultrasonographic estimation of fetal weight: development of new model and assessment of performance of previous models

A. HAMMAMI[1], A. MAZER ZUMAETA[1], A. SYNGELAKI[1], R. AKOLEKAR[2#] and K. H. NICOLAIDES[1#]

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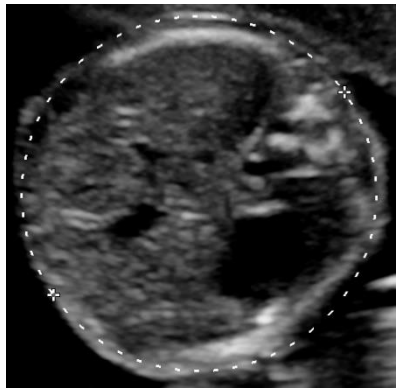
EFW centile



EFW formula

WHICH FETAL WEIGHT CENTILE CHART?

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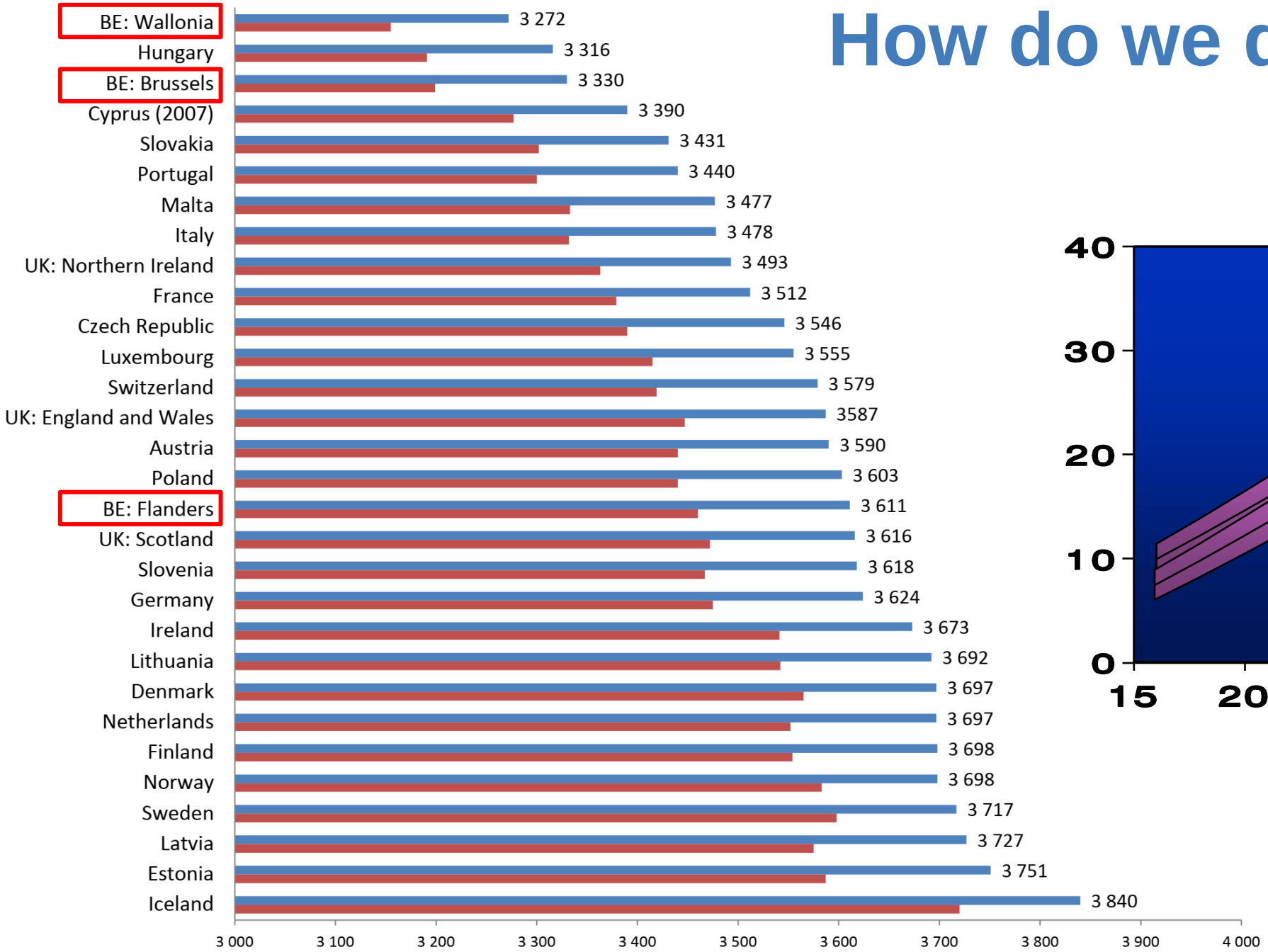
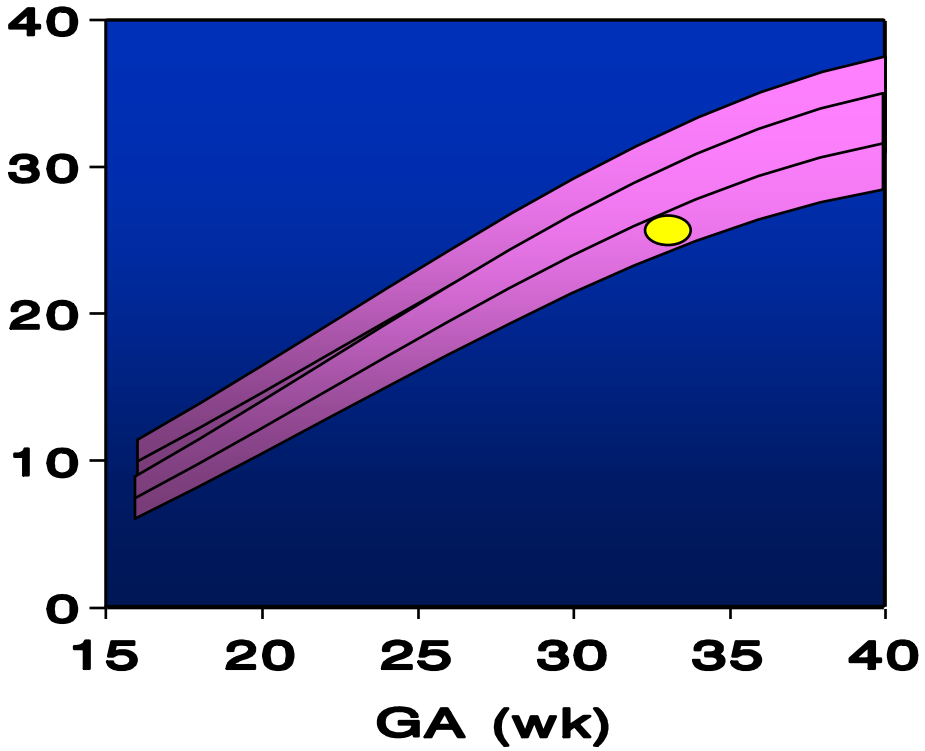
How do we define SGA?





National and regional charts

Geography and fetal growth

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Sri Lankan fetal/ birthweight charts: validation of global reference for fetal weight and birthweight percentiles

V Shanmugaraja, S G Kumarasiri, S L Wahalawatte, R V Wanigasekara, P Begam, P K C L Jayasinghe, T Padeniya, T Dias

“Only 10% of fetuses can be SGA in every country”

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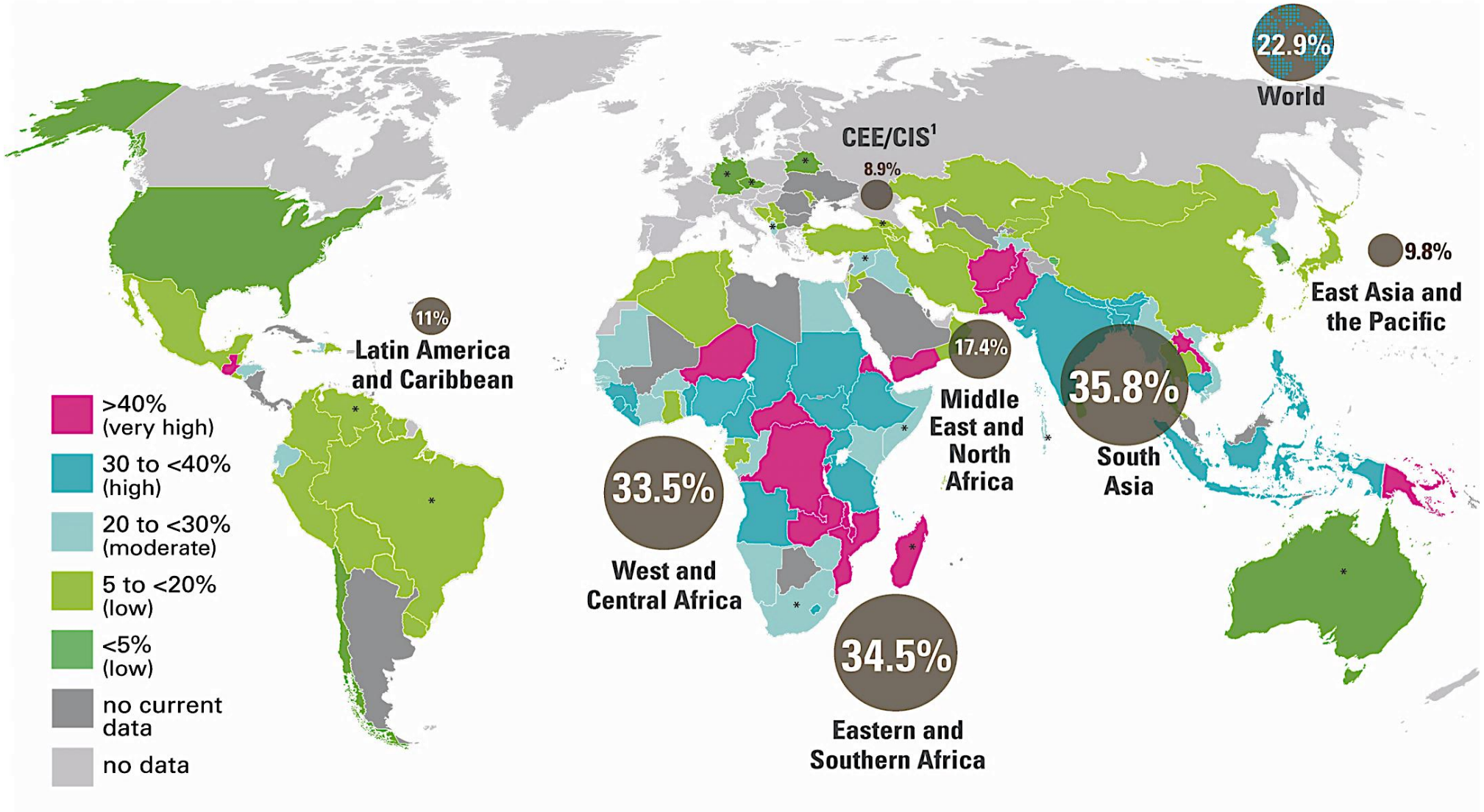

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PLOS MEDICINE

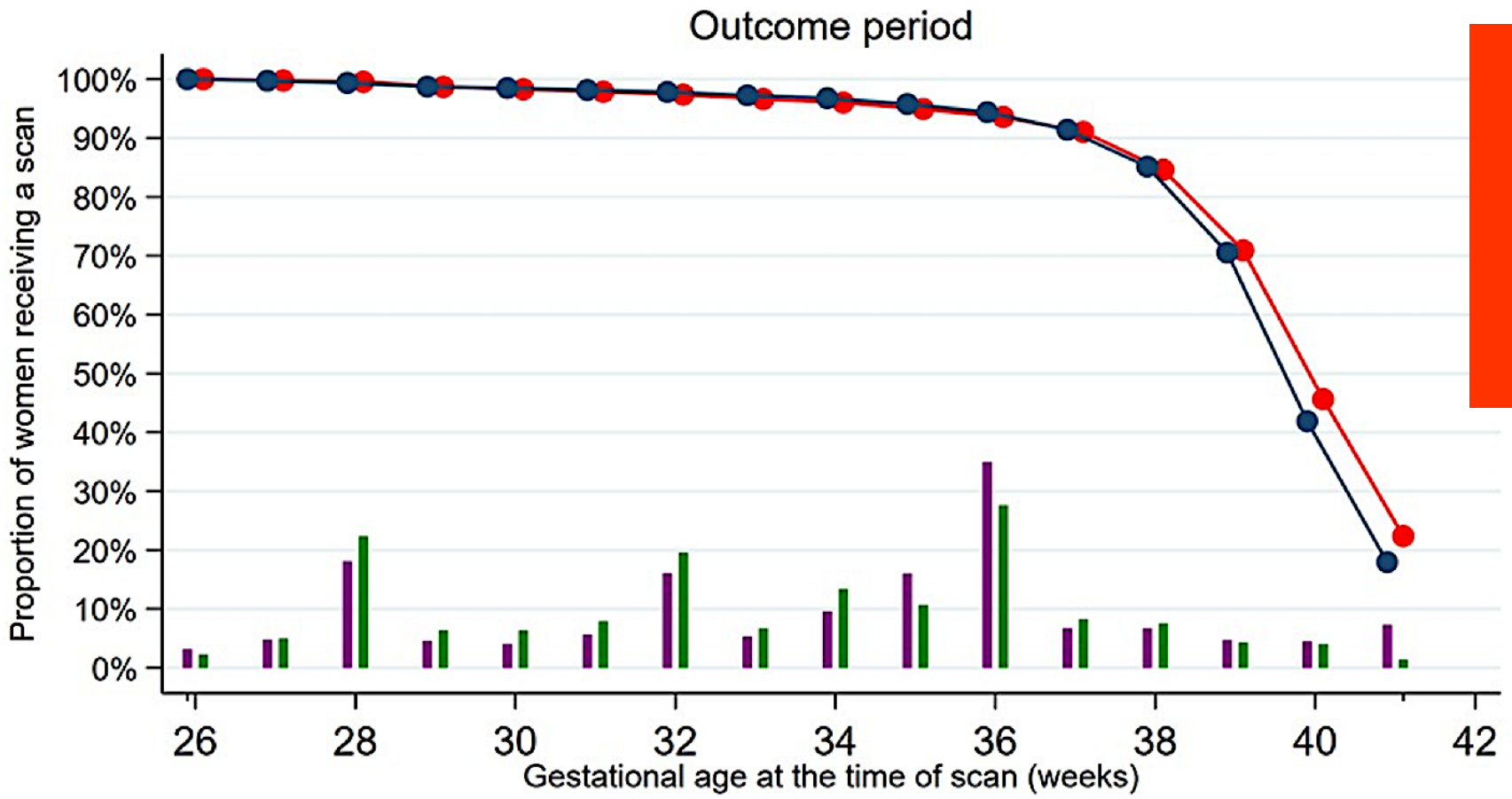
RESEARCH ARTICLE

Evaluation of the Growth Assessment Protocol (GAP) for antenatal detection of small for gestational age: The DESiGN cluster randomised trial

Matias C. Vieira[1,2], Sophie Relph[1], Walter Muruet-Gutierrez[1,3], Maria Elstad[3],

Conclusions

In this study, we observed no effect of GAP on antenatal detection of SGA compared to standard care.



"Correcting" for ethnicity did not improve SGA detection

FETAL WEIGHT AND ADVERSE OUTCOME

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Late SGA: EFW <3rd centile

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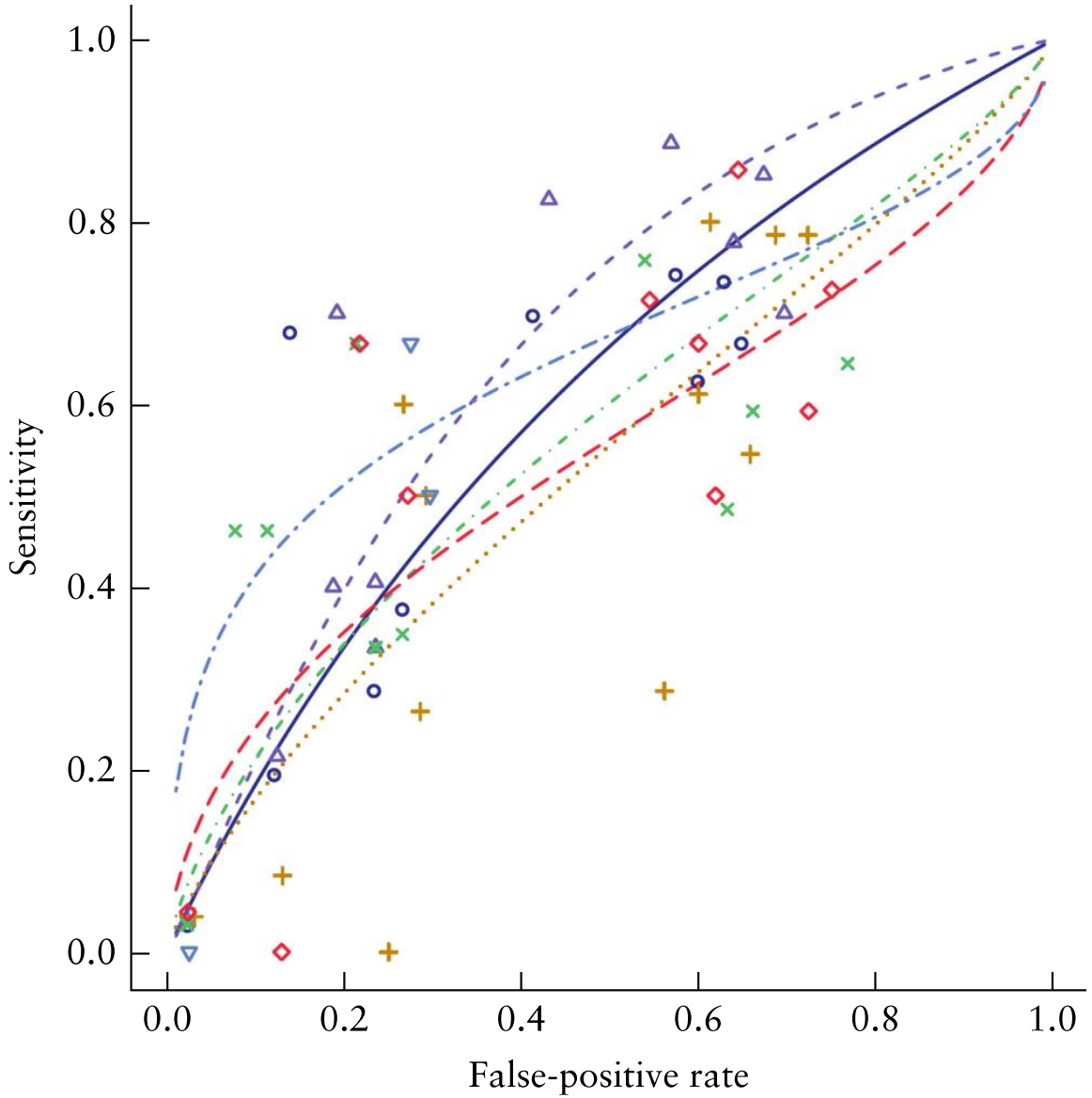
12 studies, 3639 late SGA
1246 with SGA <3rd centile

OR 1.97 for CAPO
OR 4.26 for perinatal death

Poor prediction (ROC)
AUC 0.61 for CAPO
AUC 0.65 for perinatal death



Severe smallness as predictor of adverse perinatal outcome in suspected late small-for-gestational-age fetuses: systematic review and meta-analysis

E. MELER[1#], R. J. MARTINEZ-PORTILLA[1,2#], J. CARADEUX[3], E. MAZARICO[1], C. GIL-ARMAS[1,4], D. BOADA[1], J. MARTINEZ[1], P. CARRILLO[1], M. CAMACHO[1] and F. FIGUERAS[1]

IS FETAL GROWTH VELOCITY A MORE RELIABLE MARKER FOR STILLBIRTHS?

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Late SGA: Fetal growth velocity

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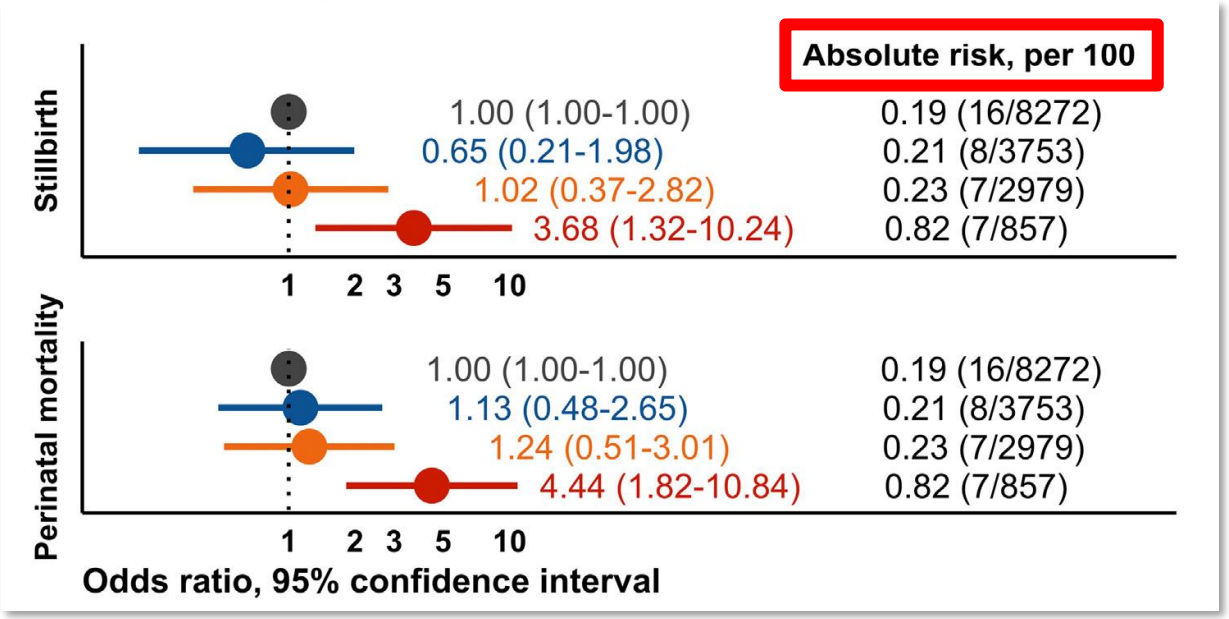
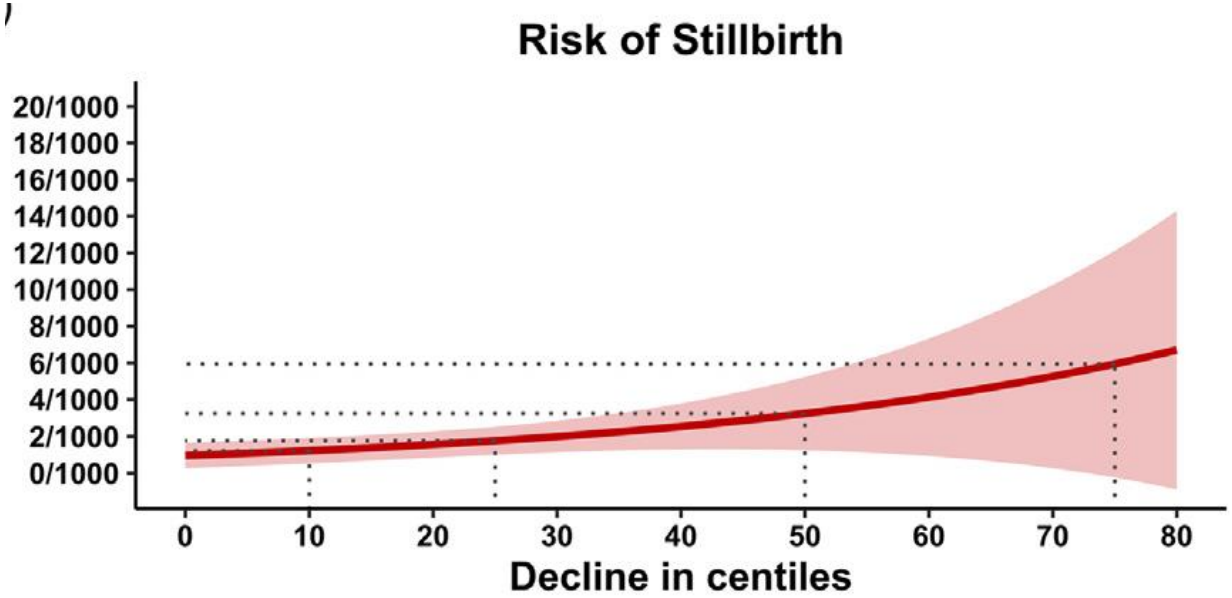


15,861 term pregnancies
28 term stillbirths (2/1000 births)
Scans at 24 and 36 weeks

Stillbirth and perinatal death only increased with a >50% decrease in growth velocity (5% FPR)



The magnitude rather than the rate of decline in fetal growth is a stronger risk factor for perinatal mortality in term infants

Mads Langager Larsen, MD; Veronika Schreiber, MClinEpi; Lone Krebs, MD, PhD; Christina Engel Hoei-Hansen, MD, PhD; Sailesh Kumar, FRCS, FRCOG, FRANZCOG, DPhil (Oxon)

WHY IS FETAL SIZE SUCH A POOR MARKER FOR STILLBIRTH AT TERM?

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Fetal chart and FGR combinations

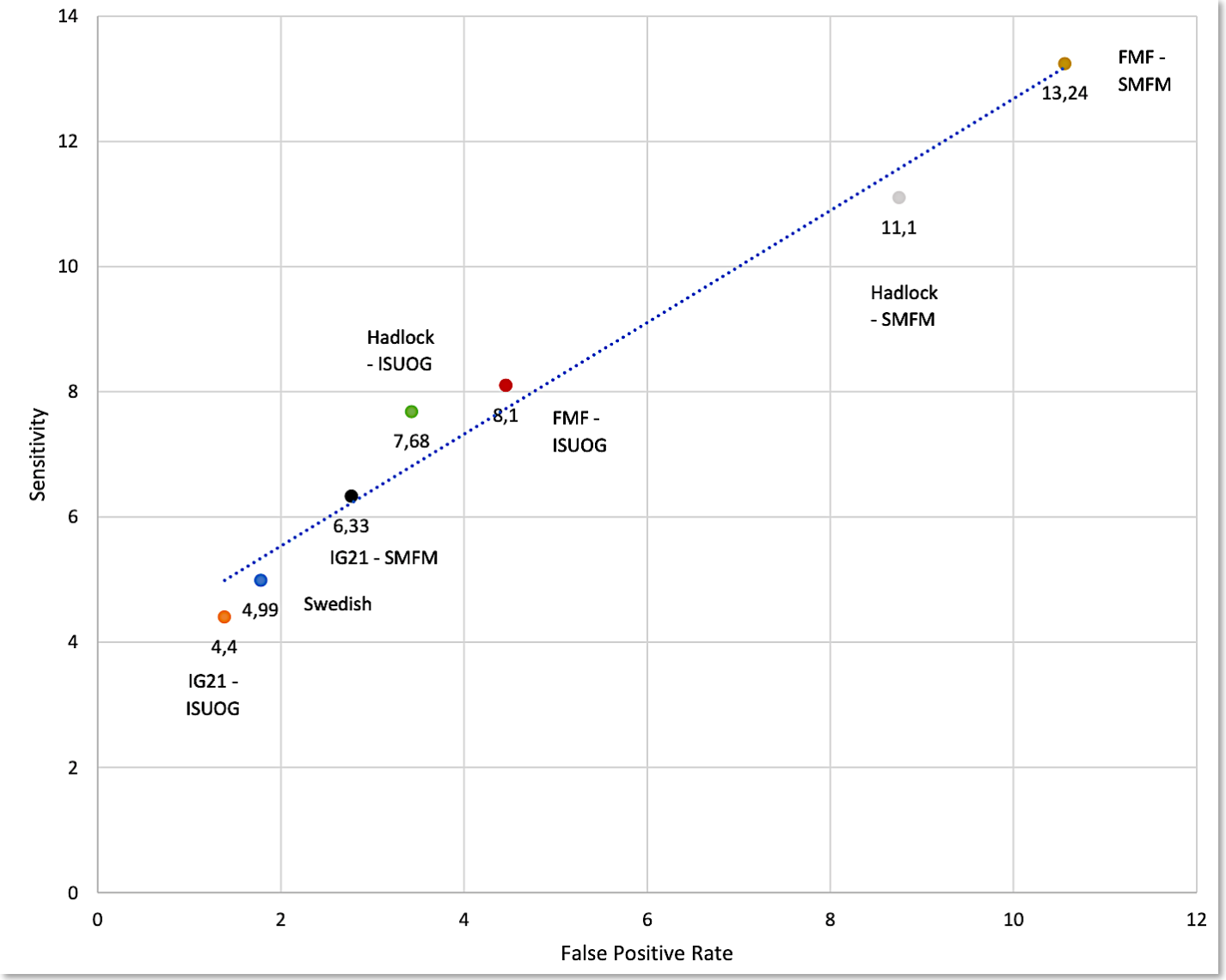
Adverse pregnancy outcome

17,261 pregnancies

EFW by: IG-21, Hadlock, FMF and Swedish

FGR by DELPHI/ISUOG, SMFM or Swedish criteria

PNM, prolonged NICU, Apgar5 <7 and HIE



Mascherpa M *et al.* UOG 2024

Birthweight and stillbirth

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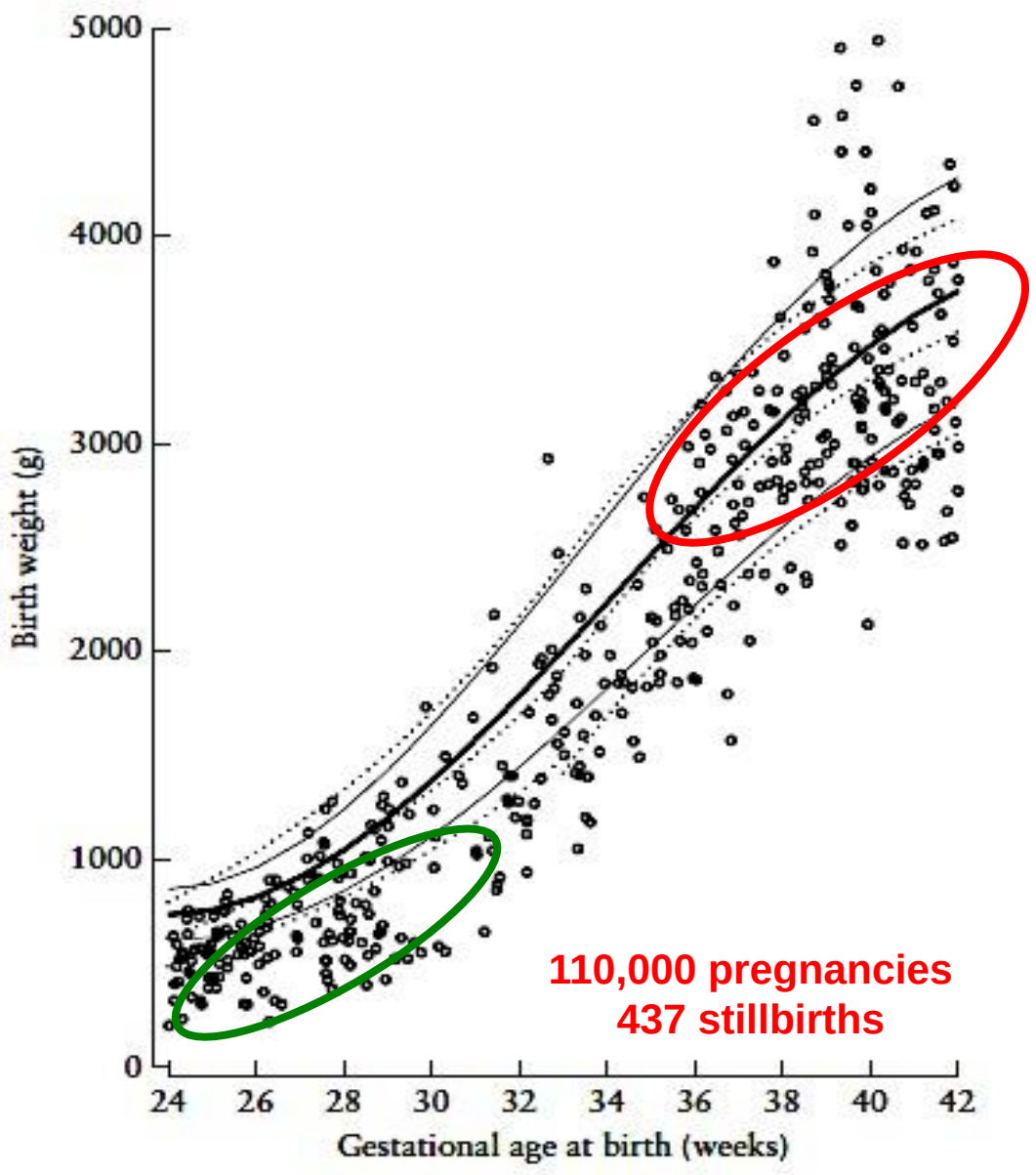
Majority of preterm stillbirths are SGA

70% of term stillbirths are <u>not</u> SGA
(67% with customisation)



Ultrasound Obstet Gynecol 2016; 48: 602–606
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.17287

Birth weight in live births and stillbirths

L. C. Y. POON*†, M. Y. TAN*, G. YERLIKAYA*, A. SYNGELAKI* and K. H. NICOLAIDES*

SGA: symptom not disease

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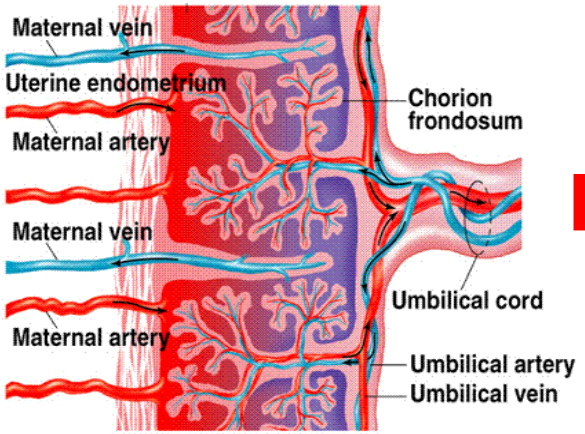

PATHOLOGY
Placental dysfunction

SYMPTOM
Slow fetal growth (Food)
Death and disability (O_2)

Stillbirth and developmental handicap occur due to hypoxaemia not malnutrition

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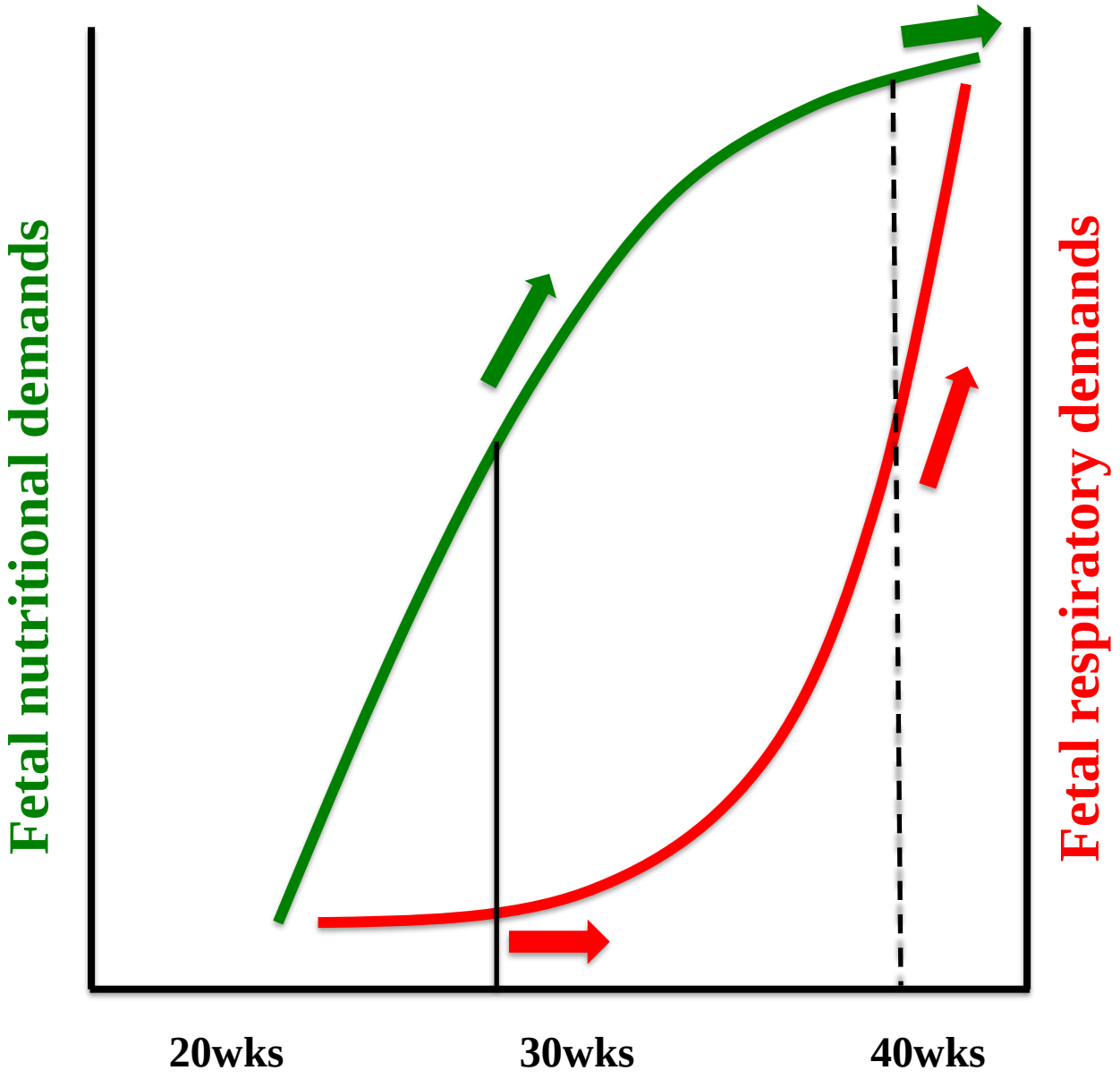
Fetal nutritional and respiratory demands increase differently with gestational age



Ultrasound Obstet Gynecol 2018; 52: 5–8
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.19110

Opinion

Ultrasound fetal weight estimation at term may do more harm than good

Dunsworth HM *et al.* PNAS 2012

Early and late FGR

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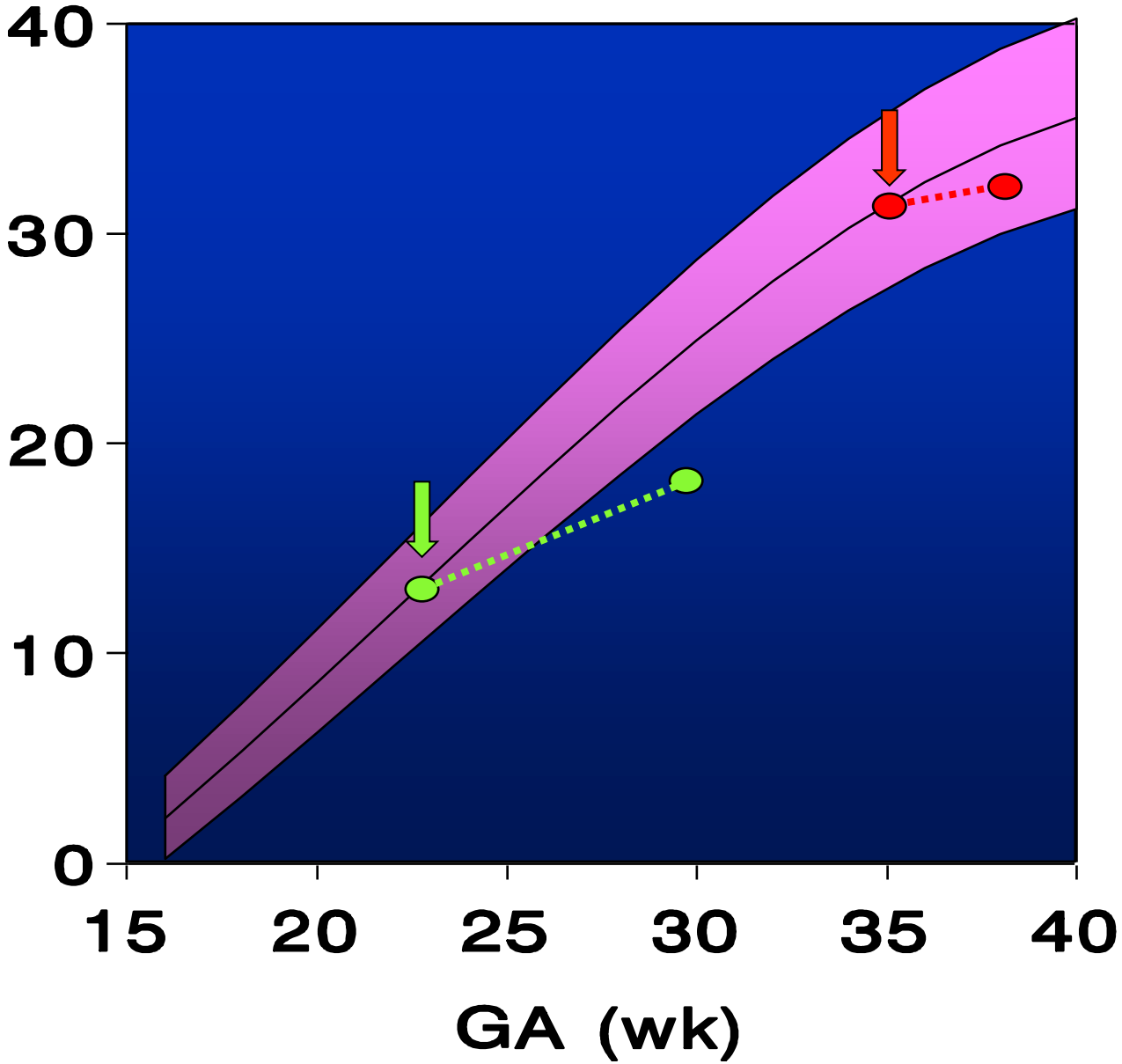
Nutrition affected most
Long latency to demise
Time for SGA to develop

Respiration affected most
Short latency to demise
SGA seen infrequently



HOW SHOULD WE MONITOR HIGH-RISK PREGNANCIES AT TERM?

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Cardiotocography

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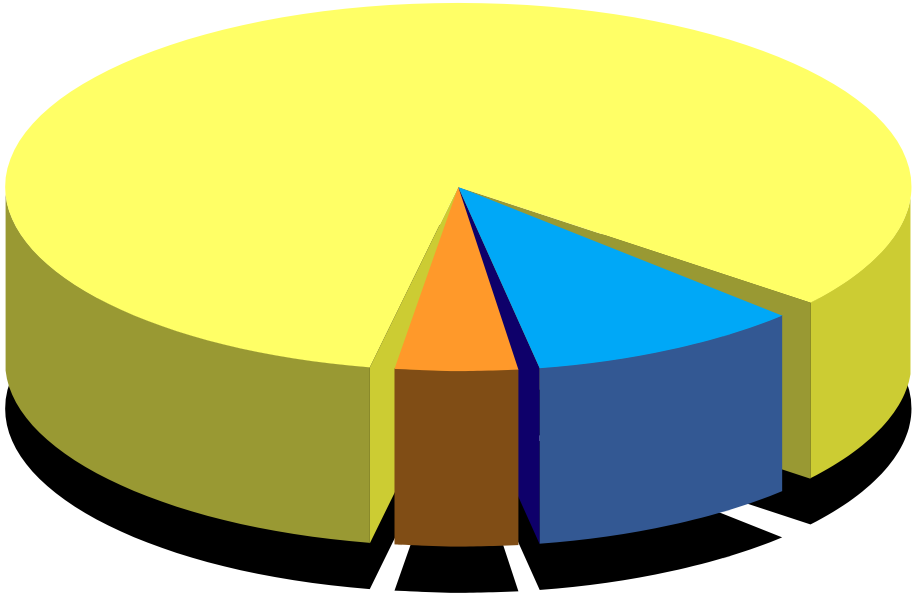
Randomised studies



9/814 PN deaths in controls

19/813 PN deaths in CTG group

- CTG interpretation
- Frequency of CTG

Conventional CTG
R=2.05 (95%CI 0.95 to 4.42)

Computerised CTG
RR=0.20 (95%CI 0.04 to 0.88)

Cochrane Database Syst Rev

CPR and Mortality

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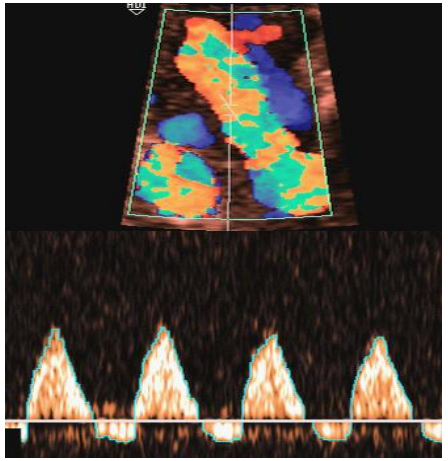
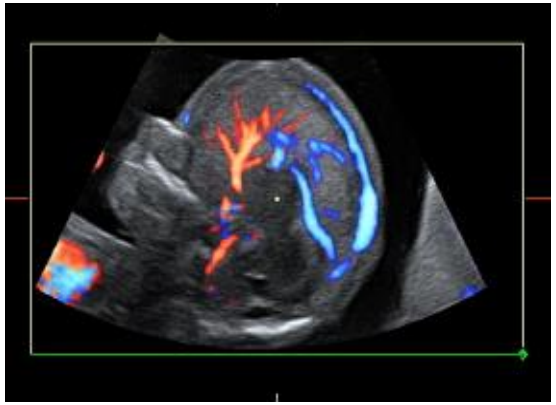
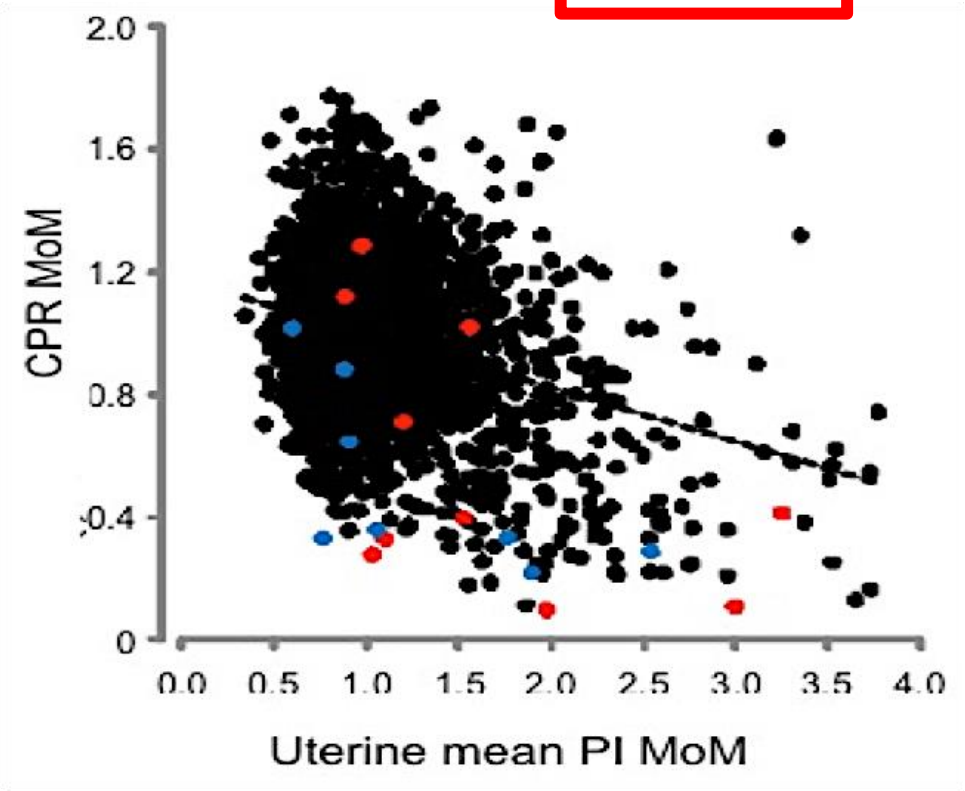
11,576 term pregnancies

Within 4 weeks of delivery

N=2832	Crude OR	p-value	Adj OR	p-value
Perinatal death (n=18)				
BW centile	0.96	<0.001	0.98	0.080
UtAD PI	3.36	<0.001	0.63	0.300
CPR MoM	0.003	<0.001	**0.004**	**<0.001**







Changes in fetal Doppler indices as a marker of failure to reach growth potential at term

J. MORALES-ROSELLÓ*†, A. KHALIL*, M. MORLANDO*, A. PAPAGEORGHIOU*, A. BHIDE* and B. THILAGANATHAN*

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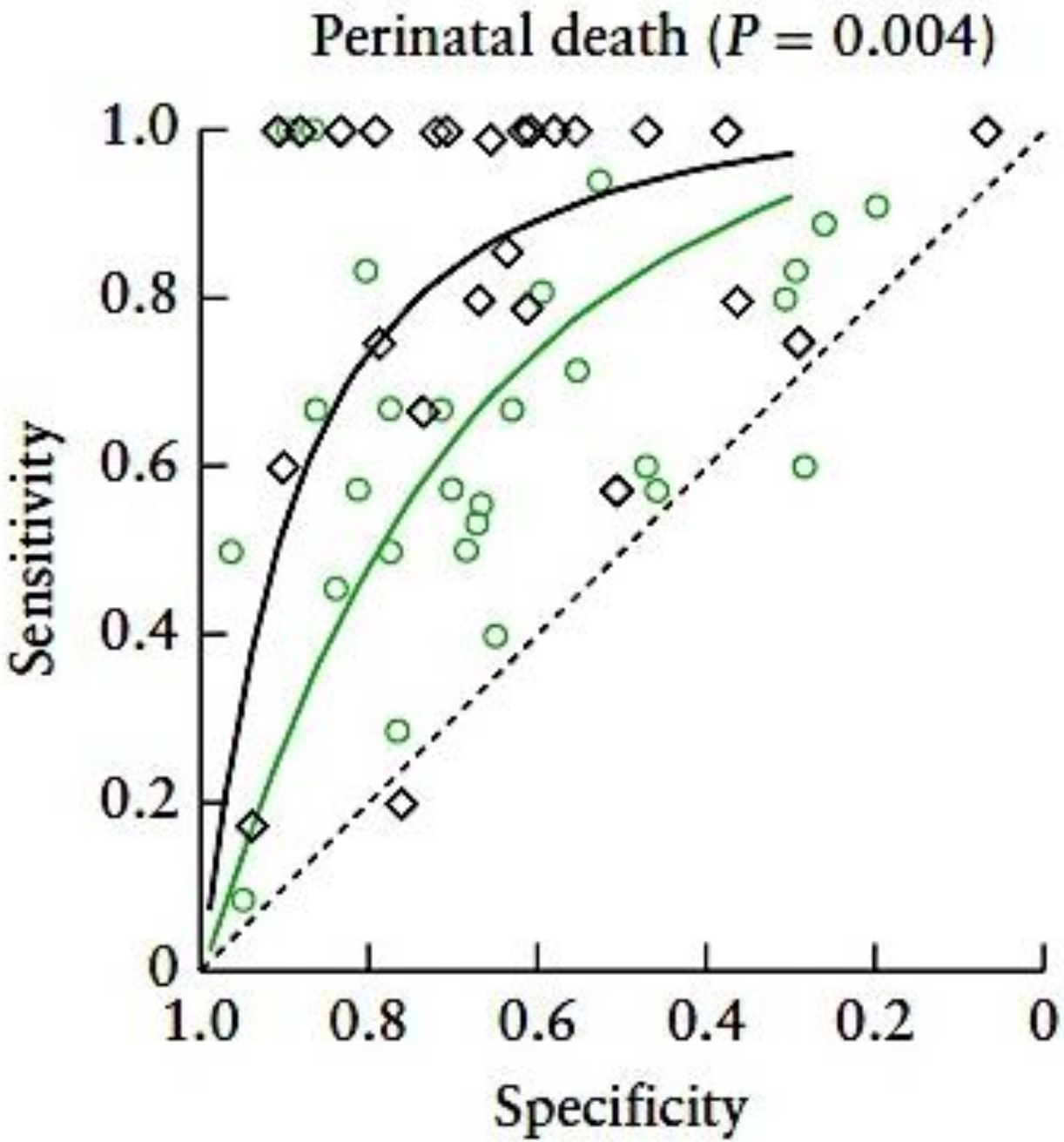
University of London

Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis

C. A. VOLLGRAFF HEIDWEILLER-SCHREURS[1], M. A. DE BOER[1], M. W. HEYMANS[2], L. J. SCHOONMADE[3], P. M. M. BOSSUYT[4], B. W. J. MOL[5,6], C. J. M. DE GROOT[1] and C. J. BAX[7]

128 studies
47,748 pregnancies

Conclusion Calculating the CPR with MCA Doppler can add value to UA Doppler assessment in the prediction of adverse perinatal outcome in women with a singleton pregnancy.



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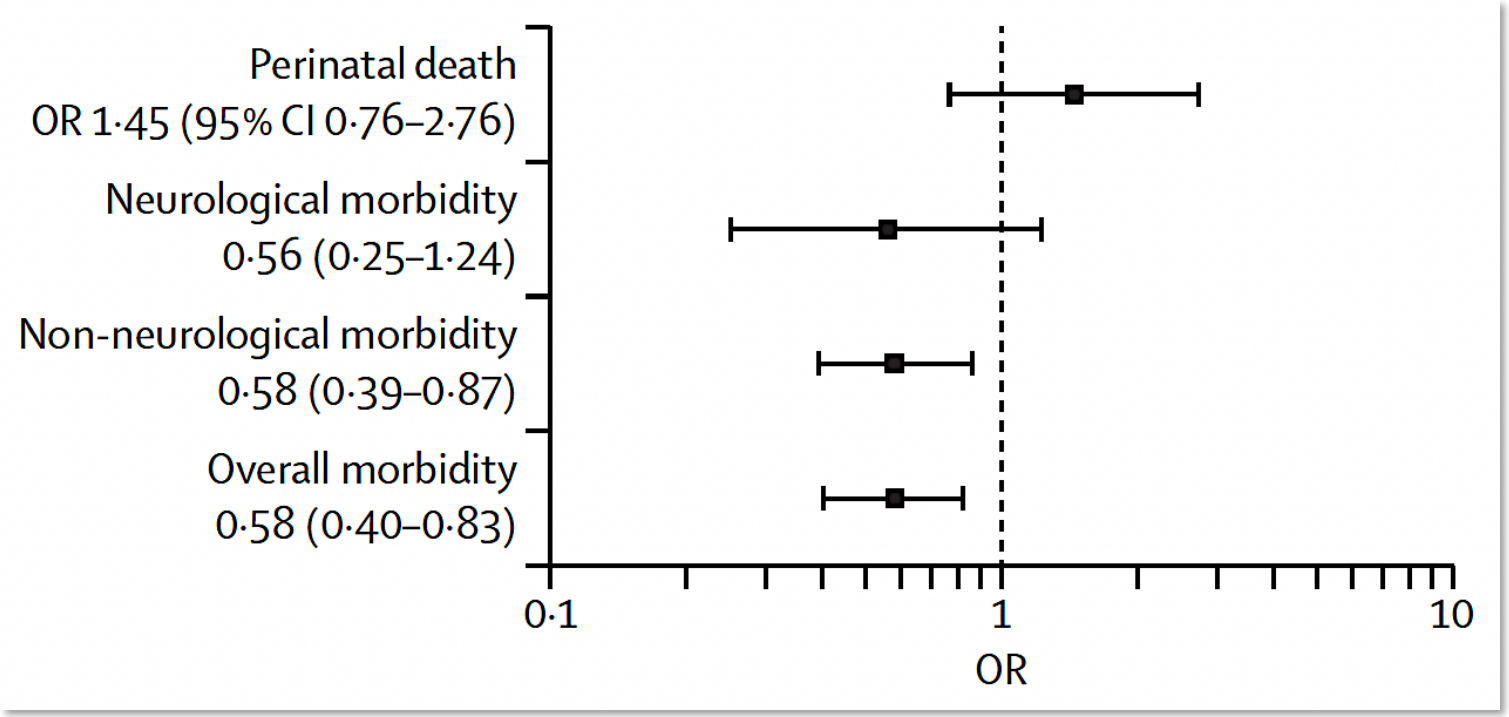
Term planned delivery based on fetal growth assessment with or without the cerebroplacental ratio in low-risk pregnancies (RATIO37): an international, multicentre, open-label, randomised controlled trial

Marta Rial-Crestelo, Marek Lubusky, Mauro Parra-Cordero, Ladislav Krofta, Anna Kajdy, Eyal Zohav, Elena Ferriols-Perez, Rogelio Cruz-Martinez, Marian Kacerovsky, Elena Scazzocchio, Lucie Roubalova, Pamela Socias, Lubomir Hašlík, Jan Modzelewski, Eran Ashwal, Julia Castellá-Cesari, Monica Cruz-Lemini, Eduard Gratacos, Francesc Figueras*, on behalf of the RATIO37 Study Group†*

9492 pregnancies scanned at 36-38 weeks

Delivery 37wks if SGA[10] and for CPR[5]



Screen 342 women

Induce 17 women

Prevent 1 severe APO

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	Concealed group (n=4774)	Revealed group (n=4718)	Risk difference* (95%CI)	p value
Perinatal death, n (%)	13 (0·3%)	13 (0·3%)	0·01 (–0·21 to 0·24)	0·98
Fetal deaths	11	8	..	..
Neonatal deaths	2	5	..	..
Severe neurological morbidity, n (%)	13 (0·3‰)	9 (0·2%)	–0·08 (–0·29 to 0·13)	0·55
IVH grade III/IV	2	0	..	..
PVL	1	0	..	..
HIE	12	9	..	..
Severe non-neurological morbidity, n (%)	23 (0·5%)	9 (0·2%)	–0·29 (–0·55 to –0·056)	0·014
Necrotising enterocolitis	1	0	..	..
Renal failure	1	0	..	..
Cardiac failure	1	0	..	..
NICU admission ≥10 days†	21	9	..	..
Overall severe morbidity, n (%)	35 (0·7%)	18 (0·4%)	–0·35 (–0·67 to –0·05)	0·022

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Routine or high-risk

Ultrasound

<10th centile

Deliver

10th-50th centile

Doppler

Low CPR

Monitor/Deliver

Normal CPR

Reassure

50th-95th centile

Reassure

>95th centile

Deliver?

Placental dysfunction at term

Summary

Stop: Checklist risk assessment

Customisation

Continue: 36-week scan

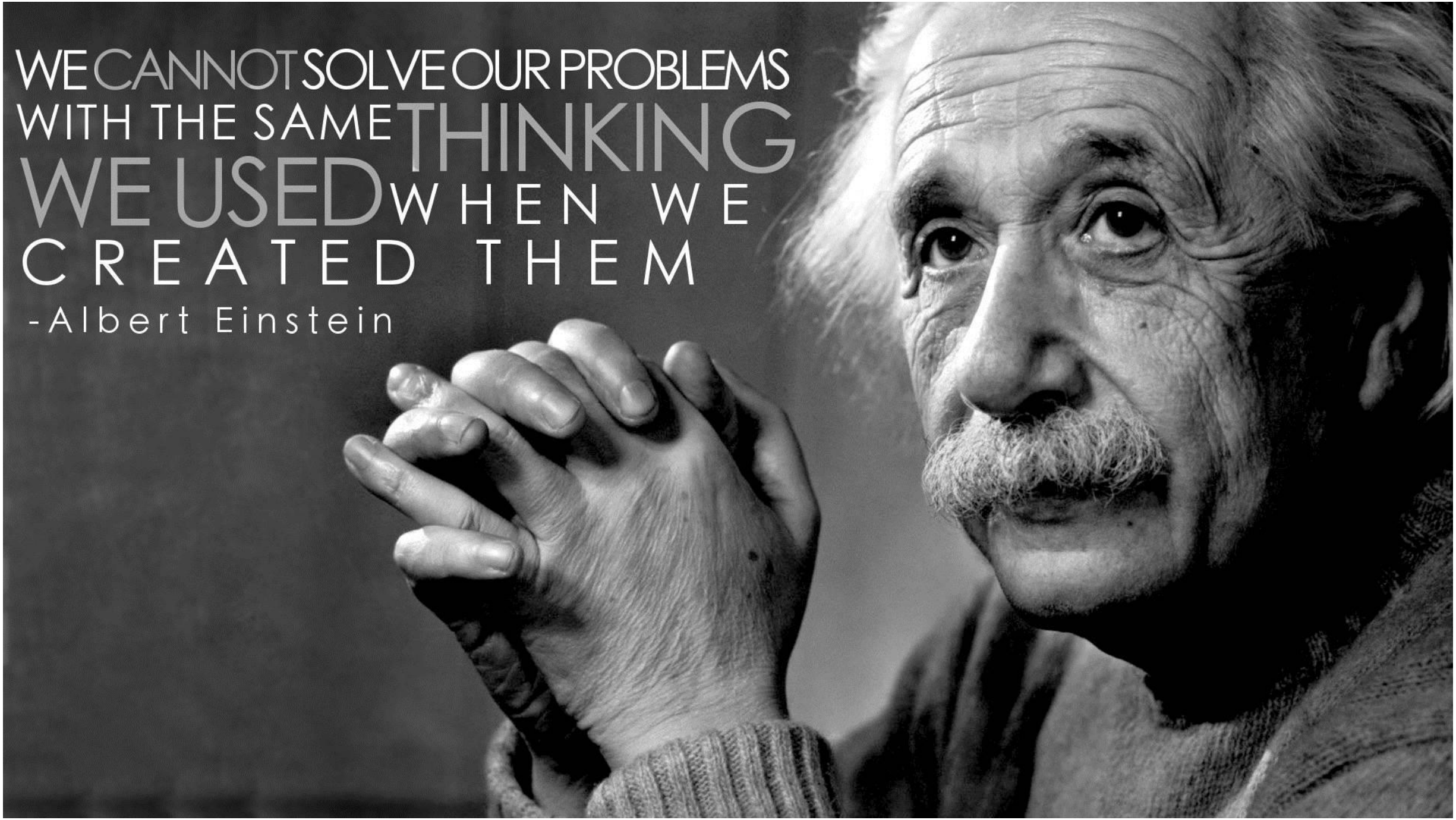
EFW Hadlock (HC, AC, FL)

EFW chart = neonatal BW chart

Consider: Deliver <3rd from 37wks

Deliver <10th from 39wks

Consider earlier birth for low CPR


WE CANNOT SOLVE OUR PROBLEMS
WITH THE SAME THINKING
WE USED WHEN WE
CREATED THEM
-Albert Einstein