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 \( \frac{1}{2} \) 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.

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

58% of total mortality

72% of mortality >36 wks

Vasak et al Ultrasound OG 2015
Perinatal mortality $\geq 36$ wks

![Graph showing perinatal mortality per 1000 births by birth weight percentile.](image-url)
Perinatal mortality $\geq 36$ 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 (i.e., 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? *Trevathan et al, Evolutionary Medicine 189, 1999

constitute a major challenge for vaginal delivery*
Infant’s death following maternal death

<table>
<thead>
<tr>
<th>Location</th>
<th>RR infant death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia; mat death &lt;42d after delivery</td>
<td>46 (25.9-81.9)</td>
</tr>
<tr>
<td>Rural South Africa</td>
<td>15.2 (8.3-27.9)</td>
</tr>
<tr>
<td>Rural Tanzania, child death &lt;10y:</td>
<td>5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Newborn weight (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>1.63 ± 0.04</td>
</tr>
<tr>
<td>MM</td>
<td>1.62 ± 0.02</td>
</tr>
<tr>
<td>PM</td>
<td>1.31 ± 0.02</td>
</tr>
<tr>
<td>MP</td>
<td>2.17 ± 0.09</td>
</tr>
</tbody>
</table>

So, for short term survival

- Birth weight should be around the 90\textsuperscript{th} 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

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

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 $\geq 36$ 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.
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)

*Third-trimester fetal Doppler in screening for adverse perinatal outcome*

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**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 3\textsuperscript{rd} trimester stillbirth

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR \textsuperscript{multivariate}</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR/SFD</td>
<td>7.0 (3.3-15.1)</td>
</tr>
<tr>
<td>Age&gt;35</td>
<td>4.1 (1.0-16.5)</td>
</tr>
<tr>
<td>BMI&gt;25</td>
<td>4.7 (1.7-10.2)</td>
</tr>
<tr>
<td>Education&lt;10 y</td>
<td>3.4 (1.2-9.6)</td>
</tr>
<tr>
<td>IUGR/BMI&gt;25</td>
<td>71 (14-350) \textsuperscript{univariate OR}</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity 0</td>
<td>1.8 (1.3-2.5)</td>
</tr>
<tr>
<td>African/Indian/Pakistani</td>
<td>2.3-3.0</td>
</tr>
<tr>
<td>BMI &gt; 35</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Pre-existing diabetes</td>
<td>3.9 (1.7-8.9)</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>3.4 (2.6-4.5)</td>
</tr>
<tr>
<td>Active smoker no FGR</td>
<td>2.5 (1.7-3.6)</td>
</tr>
<tr>
<td>Active smoker FGR</td>
<td>5.7 (3.6-8.9)</td>
</tr>
<tr>
<td>Non-smoker FGR</td>
<td>7.8 (5.6-10.9)</td>
</tr>
</tbody>
</table>
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:
  
<table>
<thead>
<tr>
<th></th>
<th>&lt;32 wks</th>
<th>32-36</th>
<th>&gt;36wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>88%</td>
<td>66%</td>
<td>43%</td>
</tr>
</tbody>
</table>

- Screening at 30-34 wks, using mat factors, EFW, UtA PI, MAP, PlGF
  Detection rate SGA < 5th centile for 10% FPR:
  
<table>
<thead>
<tr>
<th></th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>65%</td>
</tr>
</tbody>
</table>

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

Flow diagram of the trial process

Women eligible (n=1116)
- Excluded (n=466):
  - Refused use of medical data (n=14)
  - Refused randomisation (n=452):
    - Induction of labour (n=88)
    - Expectant monitoring (n=364)

Women randomised (n=650)
- Assigned to induction of labour (n=321):
  - Induction of labour (n=306)
    - Spontaneous onset of labour (n=12)
    - Planned caesarean section (n=2)
    - Unknown (n=1)
  - Unknown (n=12)

- Assigned to expectant monitoring (n=329):
  - Induction of labour (n=166)
    - Spontaneous onset of labour (n=151)
    - Planned caesarean section (n=11)
    - Unknown (n=1)

Analysed for primary outcome (n=321)
Perinatal mortality: 0

Broers et al, 2010
## DIGITAT study

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>Expect man</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>321</td>
<td>329</td>
</tr>
<tr>
<td><strong>CS</strong></td>
<td>14 %</td>
<td>13.7%</td>
</tr>
<tr>
<td>Birthweight&lt;3(^{rd}) cent</td>
<td>12.5%</td>
<td>30.6%</td>
</tr>
<tr>
<td>Birthweight&gt;25(^{th}) c</td>
<td>7.2%</td>
<td>6.1%</td>
</tr>
<tr>
<td>PNMortality</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Composite Morbidity</td>
<td>5.3%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Boers et al  BMJ 2010;341;c7087
FIGURE 4
Gestational age at randomization vs percentage of neonates with a positive MAIN score

p = 0.24

MAIN, Morbidity Assessment Index for Newborns.
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
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
Perinatal mortality singletons vs twins

Vasak et al, AJOG in press
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 in press
### Cochrane: induction vs expectant management

#### 37-40 wks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Induction  n/N</th>
<th>Expectant  n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>780</td>
<td>520</td>
<td>100.0 %</td>
<td></td>
<td>0.58 [0.34, 0.99]</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Z = 2.01, P = 0.045</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

#### >41 wks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Induction  n/N</th>
<th>Expectant  n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>3865</td>
<td>2837</td>
<td>100.0 %</td>
<td></td>
<td>0.92 [0.76, 1.12]</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Z = 1.23, P = 0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### > 42 wks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Induction  n/N</th>
<th>Expectant  n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>407</td>
<td>403</td>
<td>100.0 %</td>
<td></td>
<td>0.97 [0.72, 1.31]</td>
</tr>
</tbody>
</table>
## Magnitude of fetal death;
**singletons without cong malformations**

<table>
<thead>
<tr>
<th>Author</th>
<th>Country (y)</th>
<th>Population</th>
<th>Stillbirths</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilliod</td>
<td>USA 2005</td>
<td>3.400k</td>
<td>13.829</td>
<td>0.4%</td>
</tr>
<tr>
<td>Vasak</td>
<td>NL 2000-8</td>
<td>1.200k</td>
<td>5.048</td>
<td>0.35% (&gt;28wks)</td>
</tr>
<tr>
<td>Gardosi</td>
<td>UK 2011</td>
<td>92k</td>
<td>389</td>
<td>0.42%</td>
</tr>
</tbody>
</table>
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

Perinatal News, Autumn 2015
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     1.170k     4.119     0.35% (>28wks)
- Gardosi   UK   2011     92k     389     0.42%

Newcastle upon Tyne ( >28 wks):

<table>
<thead>
<tr>
<th>Period</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961-1980</td>
<td>2.34%</td>
</tr>
<tr>
<td>1981-2000</td>
<td>0.47%</td>
</tr>
</tbody>
</table>

Glinianaia et al, 2010
Stillbirth in relation to Perinatal death

Dutch data 2000-2008, >28wks

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

Vasak et al, U O&G, 2015
CTG-1
CTG-2
Gr1 P0, 1.66 cm, 95 kg BMI 34.5

11.40 h, 2 cm/min
Gr1 P0, 1.66 cm, 95 kg BMI 34.5

14.00 h, 2cm /min
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 $\geq 36$ 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
Human fetal growth is constrained below optimal for perinatal survival

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*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 this study was to investigate the interaction between size at birth and perinatal mortality rates. The interaction between small size at birth and perinatal mortality rates was significant (p < 0.001) for all gestational ages. The interaction between large size at birth and perinatal mortality rates was significant (p < 0.001) for all gestational ages, except for stages 1 and 2. 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. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.
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 90\textsuperscript{th} 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

(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

Ulla Sovio, Ian R White, Alison Dacey, Dharmi 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 (pinteraction=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)

(Similar data by Moraitis et al, 2014)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Proportion of total (%)</th>
<th>Stillbirth rate/1000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>100.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Smokers:</td>
<td>18.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>4.3</td>
<td>13.0</td>
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<tr>
<td>No fetal growth restriction</td>
<td>13.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Non-smokers:</td>
<td>81.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>8.3</td>
<td>18.3</td>
</tr>
<tr>
<td>No fetal growth restriction</td>
<td>68.7</td>
<td>2.1</td>
</tr>
</tbody>
</table>
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 infant’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

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
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
• 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.
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 $<25^{th}$ 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

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early preterm &lt;34 wks</td>
<td>0.8 (0.4-1.4)</td>
</tr>
<tr>
<td>Late preterm 34-37 wks</td>
<td>1.1 (0.4-3.4)</td>
</tr>
<tr>
<td>Term &gt;37 wks</td>
<td>5.2 (2.7-10.1)</td>
</tr>
</tbody>
</table>

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

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


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.
<table>
<thead>
<tr>
<th>Identification</th>
<th>Prevention mortal/morb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early IUGR</td>
<td>easy</td>
</tr>
<tr>
<td>Late IUGR/SGA</td>
<td>difficult</td>
</tr>
</tbody>
</table>
Late onset IUGR; uterine artery

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

Stage I: EFW <3rd centile or CPR <5th centile or MCA pulsatility index <5th centile (both persisting 12 h apart) or mean UtA pulsatility index >95th centile

Yes: ≥37 weeks
No: Repeat in 1 week

Stage II: UA absent EDV or Aol reversed diastolic velocities (both persisting 12 h apart)

Yes: ≥34 weeks
No: Repeat in 2–3 days

Stage III: DV pulsatility index >95th centile or UA reversed EDV (both persisting 12 h apart)

Yes: ≥30 weeks
No: Repeat in 24–48 h

Stage IV: DV absent/reversed EDV (persisting 12 h apart) or pathological CTG (reduced STV or deceleration pattern)

Yes: ≥26 weeks
No: Repeat in 12–24 h

Elective cesarean section

SGA: ≥40 weeks

Repeat in 2 weeks

Figueras & Gratacos, 2014
Decision algorithm for management of IUGR

Stage I: EFW <3rd centile or CPR <5th centile or MCA pulsatility index <5th centile (both persisting 12 h apart) or mean UtA pulsatility index >95th centile

Yes

≥37 weeks

Yes

≥34 weeks

Yes

Stage II: UA absent EDV or A0I reversed diastolic velocities (both persisting 12 h apart)

Yes

No

Repeat in 1 week

SGA: ≥40 weeks

Yes

Labor induction

No

≥37 weeks

No

Repeat in 2 weeks

Figuera & 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,................

If in doubt
Take
The baby out
Neonatal encephalopathy in term infants: independent antenatal risk factors:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low socio-economic status</td>
<td>3.60</td>
</tr>
<tr>
<td>Neurol. diseases in family</td>
<td>2.73</td>
</tr>
<tr>
<td>Pregn. after infertility treatment</td>
<td>4.43</td>
</tr>
<tr>
<td>Maternal thyroid disease</td>
<td>9.70</td>
</tr>
<tr>
<td>Pregn. induced hypertension</td>
<td>6.30</td>
</tr>
<tr>
<td>SFD &lt;3rd centile</td>
<td>38.23</td>
</tr>
<tr>
<td>SFD 3rd-9th centile</td>
<td>4.37</td>
</tr>
<tr>
<td>Antenatal haemorrhage</td>
<td>3.57</td>
</tr>
<tr>
<td>Viral infections during pregn.</td>
<td>2.97</td>
</tr>
<tr>
<td>Post term</td>
<td>13.2</td>
</tr>
</tbody>
</table>

(Badawi et al, 1999)
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

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Detection rate (95% confidence interval) for fixed FPR</th>
<th>Early Onset PE</th>
<th>Late Onset PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All n=68</td>
<td>with IUGR n=13</td>
<td>All n=99</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Maternal characteristics plus</td>
<td>40</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>47</td>
<td>62</td>
<td>69</td>
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<tr>
<td>Free β-hCG</td>
<td>38</td>
<td>56</td>
<td>46</td>
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<td>ADAM12</td>
<td>40</td>
<td>60</td>
<td>58</td>
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<tr>
<td>PI GF</td>
<td>51</td>
<td>58</td>
<td>67</td>
</tr>
<tr>
<td>MAP</td>
<td>50</td>
<td>64</td>
<td>39</td>
</tr>
<tr>
<td>Maternal characteristics plus combination of markers</td>
<td>53</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>MAP and PAPP-A</td>
<td>54</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>MAP and PI GF</td>
<td>54</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>MAP, PAPP-A and PI GF</td>
<td>54</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>MAP, PAPP-A, ADAM12 and PI GF</td>
<td>56</td>
<td>72</td>
<td>67</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Model</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>AUC (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>40</td>
<td>94.1</td>
<td>0.79 (0.692–0.888)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Glycerol and weight</td>
<td>40</td>
<td>95</td>
<td>0.796 (0.698–0.894)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Glycerol, 1-methylhistidine</td>
<td><strong>56.7</strong></td>
<td>95</td>
<td>0.783 (0.667–0.898)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Respective probability equations based on the regression analyses.

AUC, area under curve; CI, confidence interval.

a Sixty normal cases added from prior publication\textsuperscript{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.

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

Women eligible (n=1116)
- Excluded (n=466):
  - Refused use of medical data (n=14)
  - Refused randomisation (n=452):
    - Induction of labour (n=88)
    - Expectant monitoring (n=364)

Women randomised (n=650)
- Assigned to induction of labour (n=321):
  - Induction of labour (n=306)
  - Spontaneous onset of labour (n=12)
  - Planned caesarean section (n=2)
  - Unknown (n=1)
- Assigned to expectant monitoring (n=329):
  - Induction of labour (n=166)
  - Spontaneous onset of labour (n=151)
  - Planned caesarean section (n=11)
  - Unknown (n=1)

Analysed for primary outcome (n=321)
Analysed for primary outcome (n=329)
Weight at 1 y of age in relation to death due to cardiovascular disease <65 y

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 10th 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 unexplained stillbirths are (customised) IUGR, and have a small placenta:

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

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

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

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.

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 (MgSO4, Allopurinol)
So, ……………

• Easy identification
• Sufficient monitoring tools

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

Single center cohort study:
IUGR, <34 wks, Univ. Med Center Utrecht, n=180

<table>
<thead>
<tr>
<th>Variables</th>
<th>outcome</th>
</tr>
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<tbody>
<tr>
<td>Gestational age</td>
<td>Neonatal mortality</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Infant mortality</td>
</tr>
<tr>
<td>parity</td>
<td>Neonatal morbidity</td>
</tr>
<tr>
<td>Sex</td>
<td>Neur.morbidity at 2 years</td>
</tr>
<tr>
<td>Maternal disease</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>FHR pattern</td>
<td></td>
</tr>
<tr>
<td>Umbilical artery PI</td>
<td></td>
</tr>
<tr>
<td>Ductus Venosus</td>
<td></td>
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<tr>
<td>Apgar and pH at birth</td>
<td></td>
</tr>
<tr>
<td>Placenta histology</td>
<td></td>
</tr>
<tr>
<td>IVH/ROP/NEC/RDS/NICU days</td>
<td></td>
</tr>
<tr>
<td>Neonatal cranial ultrasound</td>
<td></td>
</tr>
<tr>
<td>Neurological examination at term age</td>
<td></td>
</tr>
<tr>
<td>Neurodevelopment at 2 years</td>
<td></td>
</tr>
</tbody>
</table>

Torrance et al, UOG, 2010
The graph shows the percentage of death, abnormal development (abn devel), and normal development (normal dev) across different gestational weeks (26 to 33 wks). The graph compares two conditions: Baschat and 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
Neonatal survival

Gestational week

<table>
<thead>
<tr>
<th>Week</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>1%</td>
</tr>
<tr>
<td>25</td>
<td>1%</td>
</tr>
<tr>
<td>26</td>
<td>2%</td>
</tr>
<tr>
<td>27</td>
<td>2%</td>
</tr>
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<td>28</td>
<td>2%</td>
</tr>
<tr>
<td>29</td>
<td>2%</td>
</tr>
<tr>
<td>30</td>
<td>4%</td>
</tr>
<tr>
<td>31</td>
<td>6%</td>
</tr>
<tr>
<td>32</td>
<td>8%</td>
</tr>
</tbody>
</table>

Overall mortality = 130 (21%)  
Intact survival = 352 (54%)

N=642

Baschat et al, 2007

Percent

1% / day in utero (0-1.1)

2% / day in utero (1.1-2.6)
Contribution of the different birth weight centile groups to perinatal mortality
Contribution of the different birth weight centile groups to perinatal mortality

- Weight > 90th centile: 7%
- Weight 10-90th centile: 63%
- Weight < 10th centile: 29%
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

Abnormal 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………. 
7 famine exposure groups
Birth weight and placental weight according to famine exposure

Birth weight

Placental weight
## Exposure

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Young adult</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• cong. neural def.</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ♂ obese</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>40-60 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• brain anomalies</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• schizophrenia</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• antisocial person.dis</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• major affective disorder</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• depressive symptoms</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• ↓ perceived mental health</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• ♂ obese</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• atherogenic lipid profile</td>
<td>+ (?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• BP ↑ low protein %</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• BP ↑ after stress</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• coronary heart disease</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• impaired glucose tolerance</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>• micro albuminuria</td>
<td></td>
<td>+</td>
<td>(?)</td>
</tr>
</tbody>
</table>
Or: why is human fetal growth 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

Morales-Rosello et al, 2014

SGA

AGA

LGA

art pH

ven pH
IUGR and/or low birth weight

low birth weight

Preterm

Gestational
Age

IUGR

placental
capacity

SGA

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,\textsuperscript{4} have the potential to improve pregnancy outcomes,\textsuperscript{4} 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.....
Can we diagnose fetal growth restriction from ultrasound fetal size charts?

Does the 10-90th centile range indicate normality?
Birth weight distribution

Persson et al. Diab Care 2011;34:1145-1149
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?
Perinatal mortality >28 wks, Nlds 2000-2008

- p<0.02
## Smoking, stillbirth and BW centiles;

**OR; multivariable analysis (Moriatis et al, 2014)**

<table>
<thead>
<tr>
<th>BW centile</th>
<th>smokers</th>
<th>non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>5.5</td>
<td>10.5</td>
</tr>
<tr>
<td>4-10</td>
<td>2.4</td>
<td>3.8</td>
</tr>
<tr>
<td>11-20</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>21-80</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>80-90</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>90-97</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt;97</td>
<td>4.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Overall</td>
<td>1.6 (1.4-1.8)</td>
<td></td>
</tr>
</tbody>
</table>