Early IUGR: easy to identify, difficult to treat

Late IUGR: difficult to identify, easy to treat

Differences in pathogenesis, diagnosis and management

Gerard H.A. Visser
University Medical Center Utrecht, The Netherlands
Early IUGR: easy to identify

All screening and diagnostic tests work properly
(especially Doppler umbilical artery)

Moreover, 75% of IUGR accompanied by maternal hypertensive disease
So,

• Easy identification
• Sufficient monitoring tools

• But,..... what next??
• Therapy: Oxygen?
  Corticosteroids?
  Neuroprevention (MgSO4, Allopurinol)
So, ……………

- Easy identification
- Sufficient monitoring tools

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

Neonatal survival

2% / day in utero (1.1-2.6)

1% / day in utero (0-1.1)

N=642
Overall mortality = 130 (21%)
Intact survival = 352 (54%)

Baschat et al, 2007

Percent
Gestational week

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

Baschat et al, 2007
TRUFFLE, Perinatal death & Morbidity

Antepartum deaths
2.4%
(1.3% unexpected)

Neonatal deaths
5.5%

Lees et al, U O&G Oct 2013
### Single center cohort study:
IUGR, <34 wks, Univ. Med Center Utrecht, n=180

<table>
<thead>
<tr>
<th>Variables</th>
<th>outcome</th>
</tr>
</thead>
<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>
</tr>
<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
Intact survival at 2 years:
66%
1 case of CP only
Torrance et al, 2010
%

death

abn devel

normal dev

 Baschat

TRUFFLE

26  27  28  29  30  31  32  33 wks
Brain damage in the early IUGR fetus

- is it due to hypoxaemia,
- to chronic malnutrition
- or to both
Morphological findings in human IUGR infants and in animal models

• Smaller brain size (grey matter volume), fewer cells, reduced total DNA in glial cell and neurons, deficits in synapse-to-neurone ratios, reduced dendritic growth

• Rather than localized lesions (which occur after (acute) asphyxia)

Chase et al, 1972; Dobbing, 1974; Bedi, 1984; Kreusser & Volpe, 1984; Toft et al, 1995
Morphological findings in human IUGR infants and in animal models

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

Redistribution, increased oxygen extraction, increased transport (Hb)

Chase et al, 1972; Dobbing, 1974; Bedi, 1984; Kreusser & Volpe, 1984; Toft et al, 1995
In the early IUGR fetus

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

- Which hampers adequate treatment options
All in all,

Impact of ‘adequate’ monitoring on outcome will only be limited. Prevention of IUGR / PIH that is the issue!!!
- Early identification: 12 wks: Doppler, RR, plac proteins

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

Timing of delivery

Gerard H.A. Visser
Prevention of PE with aspirin

- Meta-analysis, 31 RCTs 32,217 patients, PE 0.90 (95% CI 0.84-0.97); Askie, Lancet 2007

- Metanalysis 27 RCTs 11,348 patients, early-late start of Aspirin (Bujold et al 2010):
  - ≤ 16 wks  RR 0.47 (CI 0.34-0.65)  IUGR RR 0.44 (CI 0.30-0.65)
  - > 16 wks  RR 0.81 ns  IUGR  RR 0.98 ns

- Especially for severe PE (RR 0.09), preterm birth (RR 0.22)
<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>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stillbirth rate in relation to FGR

Gardosi et al, BMJ 2013; population based study, 389 stillbirths>24 wks (0.42%)
### Neonatal encephalopathy in term infants: independent antenatal risk factors:

<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>Pregnancy after infertility treatment</td>
<td>4.43</td>
</tr>
<tr>
<td>Maternal thyroid disease</td>
<td>9.70</td>
</tr>
<tr>
<td>Pregnancy 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 preg.</td>
<td>2.97</td>
</tr>
<tr>
<td>Post term</td>
<td>13.2</td>
</tr>
</tbody>
</table>

(Badawi et al, 1999)
Cerebral palsy in preterm and term SFD* infants; population based study; 334 infants with CP

<table>
<thead>
<tr>
<th>Preterm Group</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
Term IUGR/SGA

Morbidity is most likely to be due to a combination of malnutrition and fetal hypoxia.
Many screening and diagnostic tests do not work properly

(and that holds especially for Doppler umbilical artery)

Moreover, IUGR is not accompanied by maternal hypertensive disease
Interval Doppler – FHR changes

(Arduini; Bekedam; Hecher; Pal)
Interval Doppler – FHR changes

(Arduini; Bekedam; Hecher; Pal)
Why does Doppler not work near term?

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

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

- Late in pregnancy the fetus cannot
Term IUGR/SFD

- **Assessment techniques:**
  - Fundal height
  - Ultrasound fetal size
  - Amniotic fluid
  - Cardiotocography
  - Fetal movements!!
Structured information on fetal movements at 18 wks

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

Saastad e.s. BMC Research notes, 2010,3:2
Identification of the late IUGR fetus

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

Delivery; when?
DIGITAT study

Broers et al, 2010
## DIGITAT study

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>Expect man</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>321</td>
<td>329</td>
</tr>
<tr>
<td>CS</td>
<td>14%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Birthweight &lt; 3&lt;sup&gt;rd&lt;/sup&gt; cent</td>
<td>12.5%</td>
<td>30.6%</td>
</tr>
<tr>
<td>Birthweight &gt; 25&lt;sup&gt;th&lt;/sup&gt; 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
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.
Risk factors for 3\textsuperscript{rd} trimester stillbirth

<table>
<thead>
<tr>
<th>Risk 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
Individualize, start thinking
Perinatal mortality and birth weight centiles

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

Vasak et al, 2014
Perinatal mortality >+36 wks, Nlds 2000-2008

58% of total mortality
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.

Morales-Rosello et al, UOG 2014
And know, that...

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

Fretts and Duro, 2008
OSCAR 3

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

If in doubt
Take
The baby out
### Cochrane: induction vs expectant management

#### 37-40 wks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Induction</th>
<th>Expectant</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein 1985</td>
<td>194/491</td>
<td>164/235</td>
<td>6.2%</td>
<td>0.55 (0.20, 1.11)</td>
</tr>
<tr>
<td>Cole 1975</td>
<td>52/111</td>
<td>92/117</td>
<td>26.5%</td>
<td>0.59 (0.20, 1.67)</td>
</tr>
<tr>
<td>Egglest 1989</td>
<td>75/218</td>
<td>72/185</td>
<td>9.9%</td>
<td>0.40 (0.21, 0.81)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>780</strong></td>
<td><strong>520</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.58 [0.34, 0.99]</strong></td>
</tr>
</tbody>
</table>

#### >41 wks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Induction</th>
<th>Expectant</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augustin 1987</td>
<td>130/711</td>
<td>204/595</td>
<td>6.3%</td>
<td>0.49 (0.23, 1.02)</td>
</tr>
<tr>
<td>Chervenok 2000</td>
<td>29/134</td>
<td>20/117</td>
<td>9.3%</td>
<td>1.49 (0.92, 2.47)</td>
</tr>
<tr>
<td>Chervenok 2000</td>
<td>273/251</td>
<td>277/235</td>
<td>11.2%</td>
<td>1.23 (0.79, 1.92)</td>
</tr>
<tr>
<td>Chen 1987</td>
<td>22/152</td>
<td>211/150</td>
<td>12.6%</td>
<td>0.57 (0.32, 0.94)</td>
</tr>
<tr>
<td>Gelisom 2005</td>
<td>56/900</td>
<td>66/900</td>
<td>17.7%</td>
<td>0.48 (0.26, 0.89)</td>
</tr>
<tr>
<td>Hannam 1993</td>
<td>462/1701</td>
<td>419/704</td>
<td>30.9%</td>
<td>0.35 (0.06, 2.33)</td>
</tr>
<tr>
<td>Henry 1989</td>
<td>0/45</td>
<td>1/157</td>
<td>0.3%</td>
<td>0.15 (0.00, 1.32)</td>
</tr>
<tr>
<td>James 2001</td>
<td>31/17</td>
<td>47/37</td>
<td>1.2%</td>
<td>0.50 (0.00, 2.15)</td>
</tr>
<tr>
<td>Martin 1989</td>
<td>6/12</td>
<td>11/10</td>
<td>6.6%</td>
<td>1.65 (0.18, 16.80)</td>
</tr>
</tbody>
</table>

#### > 42 wks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Induction</th>
<th>Expectant</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergop 1986</td>
<td>27/62</td>
<td>20/64</td>
<td>38.1%</td>
<td>0.49 (0.24, 1.00)</td>
</tr>
<tr>
<td>Honrubuya 1992</td>
<td>27/57</td>
<td>24/51</td>
<td>38.0%</td>
<td>1.01 (0.68, 1.52)</td>
</tr>
<tr>
<td>Ogun 1997</td>
<td>10/27</td>
<td>3/56</td>
<td>4.3%</td>
<td>2.27 (0.95, 5.48)</td>
</tr>
<tr>
<td>Roach 1997</td>
<td>16/64</td>
<td>18/65</td>
<td>15.0%</td>
<td>0.07 (0.03, 1.80)</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**: 407/403 = 100.0%  
Risk Ratio: 0.97 [0.72, 1.31]
“I am a fetus in the womb
I fear it may become my tomb
if only I could give a shout
to get my doctor to get me out!”

a British Medical Student
High mortality/morbidity rate in the very small term babies

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

(Gardosi et al, 2005)
Late onset IUGR; uterine artery


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

<table>
<thead>
<tr>
<th>mUtA-PI z-scores</th>
<th>Third trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal (&lt;2 SD)</td>
</tr>
<tr>
<td>First trimester, normal (&lt;2 SD)</td>
<td>878</td>
</tr>
<tr>
<td>First trimester, abnormal (≥2 SD)</td>
<td>31</td>
</tr>
</tbody>
</table>

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

Cruz-Martínez, Brain Doppler and Fetal Status in Small-for-
FHR, STV, ACC and ADC in SFD/IUGR fetuses

Graatsma et al, JMFNM 2012
First trimester markers

- Maternal history
- Maternal weight
- Maternal RR
- Uterine artery PI
- Maternal serum biomarkers
Detection rate PE, with or without IUGR/SGA
maternal characteristics, MAP, serum biomarkers

<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>
</tr>
<tr>
<td>Free $\beta$-hCG</td>
<td>38</td>
<td>56</td>
<td>46</td>
</tr>
<tr>
<td>ADAM12</td>
<td>40</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>PIGF</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 PIGF</td>
<td>54</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>MAP, PAPP-A and PIGF</td>
<td>56</td>
<td>72</td>
<td>67</td>
</tr>
</tbody>
</table>

Kuc et al. PLOS One, 2013
# Metabolomics and late onset PE

## Table 4

<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>56.7</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\(^{15}\) (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
### Risk factors for 3\textsuperscript{rd} trimester stillbirth

<table>
<thead>
<tr>
<th>Risk 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)</td>
</tr>
</tbody>
</table>

\textsuperscript{univariate OR}

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

Flow diagram of the trial process
Weight at 1 y of age in relation to death due to cardiovascular disease <65 y

Osmond et al, BMJ 1993
So, for short and long term survival

- Your birth weight should be around the 90th centile
- And that also holds for weight at 1-2 y of age
- But prevent a rapid weight gain in between 2 and 7 y of age
## Risk factors for 3\textsuperscript{rd} trimester stillbirth

<table>
<thead>
<tr>
<th>Risk 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
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
On optimal fetal growth and Early and late IUGR

Gerard H.A. Visser
FIGURE
Risk of IUFD by gestational age

Nationwide data USA 2005

IUFD/10,000 Ongoing Pregnancies

Gestational Age (weeks)

IUFD, intrauterine fetal death.

Birth weight distribution

Persson et al. Diab Care 2011;34:1145-1149
On optimal fetal growth:
Which birth weight centiles are associated with the lowest perinatal mortality

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

- N=1,170,127  PNM 5.048 (0.4%)

Vasak et al, in preparation
Contribution of the different birth weight centile groups to perinatal mortality
Contribution of the different birth weight centile groups to perinatal mortality

Weight > 90\textsuperscript{th} centile: 7%
Weight 10-90\textsuperscript{th} centile: 63%
Weight < 10\textsuperscript{th} centile: 29%
Perinatal mortality >28 wks, Nlds 2000-2008

![Graph showing perinatal mortality rates by birth weight percentile.]
Perinatal mortality $\geq 36$ wks
Perinatal mortality $\geq 36$ wks
So, for short term survival

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

• Why are 90% of infants born too small?
Human fetal growth is restrained below optimal for fetal survival

Since the evolution of the large head, and changes in pelvic dimensions and orientation in association with bipedalism constitute a major challenge for vaginal delivery*

*Trevathan et al, Evolutionary Medicine 189, 1999
1342 Stillbirths > 28 wks gestation; UK

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

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

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

Vangen et al, Int J Epidemiol 2002
Birth weight and death due to cardiovascular disease <65 y of age

Osmond et al, BMJ 1993
### Chronic Heart Disease and Stroke in relation to birth weight

<table>
<thead>
<tr>
<th>Birth-Weight Category</th>
<th>Rate per 10 000 (95% CI)</th>
<th>Sex-Adjusted HR (95% CI) per kg</th>
<th>HR (95% CI) per Birth Weight z Score (n=9700)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3250 g (n=4052)</td>
<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>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>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>7.4 (2.8–26.2)</td>
<td>0.57 (0.47–0.69) P&lt;0.001</td>
<td>0.81 (0.73–0.91) P&lt;0.001</td>
</tr>
</tbody>
</table>

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

Lawlor et al, Circulation 2005
So, for short and long term survival

- Your birth weight should be around the 90th centile
- And that also holds for weight at 1-2 y of age
Birthweight, Infant growth & Type-2 diabetes

Mean Z-score

(Eriksson et al, Diab Care 2003; 26: 2006-10)
Birthweight, Infant growth & Type-2 diabetes

Mean Z-score

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

• Conflict of interest ?

• YES
Birth weight Gerry: 4 kg!
Gerry, 2+ years
Gerry, 7+ years
So, for short and long term survival

- Birth weight should be around the 90th centile

- Why?
So, for short and long term survival

- Birth weight should be around the 90th centile

- Why?

  - Because these infants had an optimal intrauterine growth, without any growth restraint