IMPAIRED FETAL GROWTH

Mario Merialdi
Office X 39
Phone 022 7913387
merialdim@who.int
Historical perspective
Public health importance

Impaired fetal growth is:
• prevalent in developing countries
• is associated with short and long term negative outcome in fetuses, infants and children
• may be associated with development of disease in adult life
Today’s approach

- Assessment fetal growth in populations
- Prevalence in different countries
- Consequences for health
- Interventions to prevent impaired fetal growth
- Further research
Characteristics of the fetus with IUGR

• Asymmetry in the dimensions of head and abdomen
• Reduced amniotic fluid
• Small placenta
Pathophysiology of impaired fetal growth

Placental insufficiency:
- Reduced transfer of nutrients
- Fetal hypoperfusion
Consequences of IUGR

• Higher perinatal morbidity and mortality
• Higher infant mortality and childhood morbidity
• Poor cognitive development and neurologic impairment
• Increased risk in adulthood of cardiovascular disease, high blood pressure, obstructive lung disease, diabetes, high cholesterol and renal damage.
Population based Perinatal mortality according to birth weight percentile:
Chile, all 262681 deliveries in 1999

<table>
<thead>
<tr>
<th>Edad gestacional (semanas)</th>
<th>&lt;p5</th>
<th>&lt;p10</th>
<th>p10-90</th>
<th>Ratio &lt;p10 / p10-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>22-25</td>
<td>1000</td>
<td>1000</td>
<td>679</td>
<td>1.5</td>
</tr>
<tr>
<td>26-29</td>
<td>616</td>
<td>519</td>
<td>288</td>
<td>1.8</td>
</tr>
<tr>
<td>30-33</td>
<td>372</td>
<td>357</td>
<td>116</td>
<td>3.1</td>
</tr>
<tr>
<td>34-36</td>
<td>168</td>
<td>128</td>
<td>30</td>
<td>4.3</td>
</tr>
<tr>
<td>37-40</td>
<td>19</td>
<td>12</td>
<td>2</td>
<td>6.0</td>
</tr>
<tr>
<td>41-43</td>
<td>14</td>
<td>10</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>62</td>
<td>3</td>
<td>20.7</td>
</tr>
</tbody>
</table>

IUGR and mortality
Assessment of fetal growth

- Retrospective assessment using anthropometric measures of size at birth (birth weight)
- Prospective assessment by serial clinical evaluations (uterine height, ultrasound measurements of fetal anatomical parameters)
Classification of fetal growth based on birth weight

• Low birth weight: < 2500 grams (does not differentiate between infants born small at term or infants small because they are preterm)

• Small for gestational age: birth weight below the the 10th percentile for a given gestational age (may erroneously categorize some normal growth newborns as growth impaired).
Figure 18
Birth weight percentiles and perinatal mortality rates (per 1000) for single female births

Note: The mean birth weight—gestational age combination is marked with a black dot. Down the right-hand side are the birth-weight-specific rates for all gestational ages, and across the top are the gestational-age-specific rates for all birth weights. The birth-weight/gestational-age-specific mortality rates, computed on the basis of 2-week gestation and 250-g weight intervals, are plotted within the square corresponding to the appropriate intersection of the birth-weight/gestational-age grid. For example, the perinatal mortality rate for infants weighing between 3251 and 3500 g and of 40 and 41 completed weeks of gestation is 3.1. The perinatal mortality rate for the birth-weight group 3251–3500 g for all gestational ages is 4.0 per 1000, and the perinatal mortality rate for the 40- to 41-week gestational age group for all birth weights is 5.0.

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* Reproduced from reference 84 with permission from the American College of Obstetricians and Gynecologists.
Reference data based on birth weight

The method is relatively easy to implement but has limitations:

• the cross sectional approach (data collected at birth from infants of different ages) may not reflect the longitudinal growth of fetuses of the same ages

• inaccuracies of estimation of gestational age at delivery affect interpretation

• pathological processes that could affect the size of infants born early in gestation
Ultrasound measurements

• Large coefficient of variation associated with estimations of fetal weight
• Margin of error in measuring individual anatomical parameters is contained
• Allow for both cross sectional and longitudinal assessment (Individualized Growth Assessment)
Internationally recommended cut-off levels for triggering public health action

- IUGR > 20%
- LBW > 15%
Estimates of impaired fetal growth in developing countries

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Source</th>
<th>%</th>
<th>Estimated total number of newborns affected per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR-LBW (&lt;2500 g; &gt;= 37 wks)</td>
<td>LBW rates from WHO data bank (1992) and regression model (Villar, 1994)</td>
<td>11</td>
<td>13,699,000</td>
</tr>
<tr>
<td>LBW &lt; 2500 g all gestaional ages</td>
<td>LBW rates from WHO data bank (1982)</td>
<td>16.4</td>
<td>20,423,000</td>
</tr>
<tr>
<td>IUGR &lt; 10 percentile all gestational ages</td>
<td>WHO collaborative study on maternal anthropometry and pregnancy outcomes (1995)</td>
<td>23.8</td>
<td>29,639,000</td>
</tr>
</tbody>
</table>
Global estimates of IUGR-LBW in developing countries (1985-1995)
IUGR-LBW

- Estimates should be viewed as conservative
- 75% of all affected newborns are born in Asia
- Rates are 6 times larger than in developed countries
- We need to improve:
  - quality and availability of birth weight data
  - assessment of gestational age
Interventions to prevent or treat impaired fetal growth
# Care and advice during pregnancy

<table>
<thead>
<tr>
<th>Intervention</th>
<th># trials</th>
<th>Participants (E+C)</th>
<th>Outcome</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuity of caregivers</td>
<td>2</td>
<td>908 + 907</td>
<td>Term - LBW</td>
<td>0.94 (0.65, 1.36)</td>
</tr>
<tr>
<td>Social support for women at risk</td>
<td>8</td>
<td>3564 + 3477</td>
<td>Term - LBW</td>
<td>0.97 (0.84, 1.13)</td>
</tr>
<tr>
<td>Own case-notes</td>
<td>2</td>
<td>276 + 276</td>
<td>Term - LBW</td>
<td>0.67 (0.35, 1.30)</td>
</tr>
<tr>
<td>Stop smoking</td>
<td>5</td>
<td>2950 + 2771</td>
<td>Term - LBW</td>
<td>0.80 (0.65, 0.98)</td>
</tr>
<tr>
<td>Nutritional advice</td>
<td>1</td>
<td>265 + 250</td>
<td>SGA</td>
<td>1.00 (0.48, 2.08)</td>
</tr>
</tbody>
</table>
**Antimalarial chemoprophylaxis**

<table>
<thead>
<tr>
<th>Intervention</th>
<th># trials</th>
<th>Participants (E+C)</th>
<th>Outcome</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All parities</td>
<td>5</td>
<td>1453 + 1616</td>
<td>MBW</td>
<td>23g (-13, 59)</td>
</tr>
<tr>
<td>Multigravida</td>
<td>2</td>
<td>342 + 362</td>
<td>MBW</td>
<td>65g (4, 125)</td>
</tr>
<tr>
<td>Primigravida</td>
<td>4</td>
<td>295 + 340</td>
<td>MBW</td>
<td>112g (41, 183)</td>
</tr>
</tbody>
</table>
## Nutritional interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th># trials</th>
<th>Participants (E+C)</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balanced protein energy</td>
<td>6</td>
<td>2147 + 2123</td>
<td>SGA</td>
<td>0.68 (0.57, 0.80)</td>
</tr>
<tr>
<td>Isocaloric balanced protein</td>
<td>1</td>
<td>391 + 391</td>
<td>SGA</td>
<td>1.35 (1.12, 1.61)</td>
</tr>
<tr>
<td>High protein</td>
<td>1</td>
<td>249 + 256</td>
<td>SGA</td>
<td>1.58 (1.03, 2.51)</td>
</tr>
<tr>
<td>Salt restriction</td>
<td>1</td>
<td>110 + 132</td>
<td>SGA</td>
<td>1.50 (0.73, 3.07)</td>
</tr>
<tr>
<td>Salt restriction</td>
<td>1</td>
<td>184 + 177</td>
<td>LBW</td>
<td>0.84 (0.42, 1.67)</td>
</tr>
</tbody>
</table>
## Nutritional interventions

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<tr>
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<th>Participants (E+C)</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>1</td>
<td>97 +93</td>
<td>SGA</td>
<td>0.72 (0.26, 1.99)</td>
</tr>
<tr>
<td>Calcium</td>
<td>7</td>
<td>3230 + 3261</td>
<td>LBW</td>
<td>0.83 (0.71, 0.98)</td>
</tr>
<tr>
<td>Folate</td>
<td>5</td>
<td>754 +734</td>
<td>LBW</td>
<td>0.75 (0.50, 1.12)</td>
</tr>
<tr>
<td>Iron selective vs. routine</td>
<td>1</td>
<td>50 + 50</td>
<td>SGA</td>
<td>1.60 (0.56, 4.56)</td>
</tr>
</tbody>
</table>
## Nutritional interventions

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<tr>
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<th># trials</th>
<th>Participants (E+C)</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>3</td>
<td>865 + 876</td>
<td>SGA</td>
<td>0.70 (0.53, 0.93)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>4</td>
<td>968 + 986</td>
<td>LBW</td>
<td>0.67 (0.46, 0.96)</td>
</tr>
<tr>
<td>Zinc</td>
<td>3</td>
<td>909 + 931</td>
<td>SGA</td>
<td>0.90 (0.64, 1.28)</td>
</tr>
<tr>
<td>Zinc</td>
<td>5</td>
<td>750 + 722</td>
<td>LBW</td>
<td>0.77 (0.56, 1.06)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>1</td>
<td>67 + 59</td>
<td>SGA</td>
<td>0.54 (0.26, 1.10)</td>
</tr>
</tbody>
</table>
Most interventions aimed to prevent or treat impaired fetal growth do not show significant effects on short term perinatal outcomes
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

- Epidemiological associations versus effectiveness of pragmatic interventions
- Timing of the “insult” versus different fetal organ growth patterns
- Timing and site of nutrient deposition in the mothers and the effect on fetal growth
- Interpretation of the results of randomized clinical trials of maternal nutritional interventions
- Intervention specific outcomes versus morbidity/mortality/birth weight outcomes
- Length and “dose” of nutritional supplementation
- Pharmacological effect versus nutritional effect
- Heterogeneity of outcomes

Timing and site of nutrient deposition in the mothers and the effect on fetal growth

Interpretation of the results of randomized clinical trials of maternal nutritional interventions

Epidemiological associations versus effectiveness of pragmatic interventions

Timing of the “insult” versus different fetal organ growth patterns

Length and “dose” of nutritional supplementation

Pharmacological effect versus nutritional effect

Heterogeneity of outcomes
Epidemiological association vs. effectiveness of pragmatic interventions

• Results from observational studies or uncontrolled observations are likely to be confounded by the effect of population characteristics

• Women from disadvantaged populations are more at risk for nutritional deficiencies as well as for pregnancy complications

• Intervention groups may be better off and have better outcomes
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

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- Length and "dose" of nutritional supplementation
- Pharmacological effect versus nutritional effect
- Heterogeneity of outcomes
Timing of the insult and different fetal organ growth patterns

• Fetal organs show differential growth patterns and contribute differently to total fetal volume at different gestational ages (eg.: relationship between head and abdomen)

• The effect of a nutritional deficiency or nutritional intervention on the growth of a fetal organ is likely to be related to the timing of the insult during gestation
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

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- Interpretation of the results of randomized clinical trials of maternal nutritional interventions
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- Length and “dose” of nutritional supplementation
- Pharmacological effect versus nutritional effect
- Intervention specific outcomes versus morbidity/mortality/birth weight outcomes
- Heterogeneity of outcomes

Timing and site of nutrient deposition in the mothers and the effect on fetal growth
Timing of nutrient deposition in the mother and the effect on fetal growth

- Differential timing of nutrient deposition and its body location may also influence nutrient transfer to the fetus
- Birth weight is associated more with maternal changes in thigh skinfolds and early gestation fat gain than with other body sites or pregnancy times
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

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- Timing of the "insult" versus different fetal organ growth patterns
- Length and "dose" of nutritional supplementation
- Pharmacological effect versus nutritional effect
- Interpretation of the results of randomized clinical trials of maternal nutritional interventions
- Timing and site of nutrient deposition in the mothers and the effect on fetal growth
- Intervention specific outcomes versus morbidity/mortality/birth weight outcomes
- Heterogeneity of outcomes
Length and amount of nutritional supplementation

• It is unrealistic to assume that chronic undernutrition during two or three decades of life will be overcome, in terms of reproductive performance with only a few months of extra nutrient intake

• Energy supplementation was more effective on birth weight if it was provided for two consecutive pregnancies than during only one pregnancy
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

- Epidemiological associations versus effectiveness of pragmatic interventions
- Timing of the ”insult” versus different fetal organ growth patterns
- Interpretation of the results of randomized clinical trials of maternal nutritional interventions
- Timing and site of nutrient deposition in the mothers and the effect on fetal growth
- Length and “dose” of nutritional supplementation
- Pharmacological effect versus nutritional effect
- Intervention specific outcomes versus morbidity/mortality/birth weight outcomes
- Heterogeneity of outcomes
Pharmacological vs. Nutritional effect

- Nutrients can be provided to population with dietary deficiency (nutritional effect) or to population with adequate intake (pharmacological effect)
- Calcium supplementation for the prevention of preeclampsia seems to be effective in low calcium intake women but not in adequate calcium intake women.
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

- Epidemiological associations versus effectiveness of pragmatic interventions
- Timing of the "insult" versus different fetal organ growth patterns
- Timing and site of nutrient deposition in the mothers and the effect on fetal growth
- Interpretation of the results of randomized clinical trials of maternal nutritional interventions
- Length and "dose" of nutritional supplementation
- Pharmacological effect versus nutritional effect
- Intervention specific outcomes versus morbidity/mortality/birth weight outcomes
- Heterogeneity of outcomes
Intervention specific outcomes

• It is important to identify the most specific outcome in reference to the nutrient being evaluated

• Zinc supplementation did not increase birthweight but had a positive effect on femur length measured by ultrasonography

• “Birth weight may be too crude a marker to capture the range of all possible uterine exposure and experiences”
Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy

- Epidemiological associations versus effectiveness of pragmatic interventions
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- Length and "dose" of nutritional supplementation
- Pharmacological effect versus nutritional effect
- Intervention specific outcomes versus morbidity/mortality/birth weight outcomes
- Heterogeneity of outcomes
Heterogeneity of outcomes

• Low birth weight and small for gestational age includes conditions with different aetiologies.
• These outcomes may be too comprehensive to be significantly affected by a single nutritional intervention
Further research

• Extend the duration of nutritional supplementation interventions and follow up (Barker hypothesis)
• Identify new outcomes and evaluate their biological and clinical relevance
• Evaluate combinations of interventions
• Develop mechanistic hypotheses
• Identify the determinants of fetal growth (genetics vs. environment) and develop standards of fetal growth for international applications
• Individualised Growth Assessment
Individualised Growth Assessment

• Each fetus serves as its own control
• The expected normal range of growth is determined by an equation using measurements from two fetal biometry assessments performed during the second trimester
• Takes into account the fetal growth potential of each individual fetus
**Review:** Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems  
**Comparison:** 02 Routine calcium supplementation in pregnancy by baseline dietary calcium  
**Outcome:** 02 Pre-eclampsia

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk (Random)</th>
<th>Weight %</th>
<th>Relative Risk (Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Adequate calcium diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPEP 1997</td>
<td>158 / 2163</td>
<td>168 / 2173</td>
<td>19.2</td>
<td>0.94</td>
<td>[0.77, 1.16]</td>
</tr>
<tr>
<td>Crowther 1999</td>
<td>10 / 227</td>
<td>23 / 229</td>
<td>14.7</td>
<td>0.44</td>
<td>[0.21, 0.90]</td>
</tr>
<tr>
<td>Villar 1987</td>
<td>1 / 25</td>
<td>3 / 27</td>
<td>4.7</td>
<td>0.36</td>
<td>[0.04, 3.24]</td>
</tr>
<tr>
<td>Villar 1990</td>
<td>0 / 90</td>
<td>3 / 88</td>
<td>2.9</td>
<td>0.14</td>
<td>[0.01, 2.67]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>169 / 2505</td>
<td>197 / 2517</td>
<td>41.5</td>
<td>0.62</td>
<td>[0.32, 1.20]</td>
</tr>
</tbody>
</table>
| Test for heterogeneity chi-square=6.20 df=3 p=0.1024  
Test for overall effect Z=-1.43 p=0.15 |
| 03 Low calcium diet |           |         |                        |          |                        |
| Belizan 1991   | 15 / 579  | 23 / 588 | 15.5                   | 0.66     | [0.35, 1.26]           |
| L-Jaramillo 1989 | 2 / 55   | 12 / 51  | 8.3                    | 0.15     | [0.04, 0.66]           |
| L-Jaramillo 1990 | 0 / 22   | 8 / 34   | 3.2                    | 0.09     | [0.01, 1.48]           |
| L-Jaramillo 1997 | 4 / 125  | 21 / 135 | 11.5                   | 0.21     | [0.07, 0.58]           |
| Puwar 1996     | 2 / 97    | 11 / 93  | 8.0                    | 0.17     | [0.04, 0.77]           |
| S-Ramos 1994   | 4 / 29    | 15 / 34  | 12.0                   | 0.31     | [0.12, 0.84]           |
| Subtotal (95% CI) | 27 / 907  | 90 / 935 | 58.5                   | 0.29     | [0.16, 0.54]           |
| Test for heterogeneity chi-square=8.04 df=5 p=0.1540  
Test for overall effect Z=4.00 p=0.00 |
| Total (95% CI) |           |         |                        |          |                        |
|                | 196 / 3412| 287 / 3452| 100.0                  | 0.37     | [0.21, 0.64]           |
| Test for heterogeneity chi-square=28.67 df=9 p=0.0007  
Test for overall effect Z=3.57 p=0.00 |
Reduced transfer of nutrients

• Abnormalities of the placenta lead to increased resistance of blood flow in the placenta

• Increased resistance determines a reduction of flow through the placenta

• the fetus reacts to a condition of limited supply of nutrients and oxygen by vascular redistribution that spares vital organs (brain, myocardium, adrenal glands).