Intrauterine Growth Retardation and Insulin resistance

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Normal Fetal Growth

- The dominant determinants of fetal growth:
- The integrity of the materno-placento-fetal unit
- The adequate nutrient supply
- The adequate hormonal milieu:
  - IGF-I, IGF-II, insulin
IUGR

**Definition**

The term *intra-uterine growth retardation* is assigned to infants with a birth weight and/or length <10th percentile for gestational age, with a pathologic restriction of fetal growth.
Causes of IUGR

- **Maternal**
  - Medical complications (↑BP, asthma etc)
  - Environmental (smoking, alcohol etc)

- **Fetal**
  - Genetic (chromosomal abnormalities etc)
  - Infections (TORCH)
  - Malformations (cardiovascular, skeletal, etc)

- **Placental**
  - (Reduced blood flow, abnormal placentation,..)

- **Hormonal**
# IUGR: Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Symmetric</th>
<th>Asymmetric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Cause</td>
<td>intrinsic</td>
<td>extrinsic</td>
</tr>
<tr>
<td>Gestational age</td>
<td>&lt; 28 week</td>
<td>&gt; 28 week</td>
</tr>
<tr>
<td>Cell number</td>
<td>↓ normal</td>
<td>normal</td>
</tr>
<tr>
<td>Cell size</td>
<td>normal</td>
<td>↓</td>
</tr>
<tr>
<td>Head circumference</td>
<td>↓</td>
<td>normal</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>normal</td>
<td>↓</td>
</tr>
<tr>
<td>„catch-up growth“</td>
<td>rare</td>
<td>common</td>
</tr>
</tbody>
</table>
Fetal Origin of Adult Disease

- Many epidemiological studies in the last years have demonstrated an association between
- IUGR and
- The metabolic syndrome, i.e. Hyperlipidemia, DM type 2, cardiovascular disease, arterial hypertension
IUGR: Barker’s Hypothesis (1)

- **The thrifty phenotype hypothesis.**
- The growth of the fetus is determined by its nutritional environment. In cases of nutrient restriction, the adverse intra-uterine environment drives a reprogramming of the endocrine-metabolic status of the fetus.
The reprogramming of the endocrine-metabolic system of the nutrient-restricted fetus is beneficial at the short-term, allowing survival, but can be detrimental at the long-term, especially if nutrient supply becomes abundant, leading to the development of the metabolic syndrome.
Maternal Undernutrition

Fetal undernutrition

Organ malfunction e.g. liver

Hyperlipidemia

\[ \downarrow \beta \text{ cell mass} \]

Insulin resistance

Abnormal Vascular development

DM type 2

\[ \uparrow \text{BP} \]

METABOLIC SYNDROME

Barker
Reprogramming of the endocrine-metabolic system

Change of the set point of the HPA Axis

↑ Cortisol

Insulin resistance

Endothelial dysfunction
Activation of HPA-axis in IUGR

**Animal data**
- In rats, intrauterine stress drives activation of HPA-axis

**In humans**
- Newborns with IUGR demonstrate:
  - ↑ Umbilical cord cortisol levels
  - ↑ Steroids excretion in childhood
  - ↑ Morning cortisol in adulthood
"The Fetal Insulin Hypothesis"

- Genes that determine insulin secretion and action and predispose to insulin resistance may lead:
  - Prenatally to intrauterine growth retardation
  - Postnatally to insulin resistance and its consequences (Metabolic syndrome)
## Insulin-Insulin Signaling Pathway

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Defect</th>
<th>Insulin</th>
<th>Birthweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucokinase deficiency</td>
<td>Mutation</td>
<td>↓ secretion</td>
<td>↓</td>
</tr>
<tr>
<td>Pancreatic agenesis</td>
<td>Mutation in IPF 1</td>
<td>No secretion</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>Transient neonatal diabetes</td>
<td>Paternal iso-disomy/dupl 6q22-q33</td>
<td>↓ ↓ secretion</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>Leprechaunism</td>
<td>IR Mutation</td>
<td>Pronounced resistance</td>
<td>↓↓↓↓</td>
</tr>
</tbody>
</table>
Intrauterine environment

Genetic factors

Small, underweight babies

Intrauterine undernutrition

Genes predisposing to insulin resistance

Intrauterine programming

Insulin resistance

Metabolic syndrome

Direct action
Since **insulin resistance** plays a key role in the pathogenesis of the metabolic syndrome can it be modified or at least prevented?
Adiponectin

- Is produced by adipocytes during their differentiation
- Its secretion is stimulated by insulin
- Low adiponectin levels are correlated with insulin resistance and precede the occurrence of Diabetes mellitus type 2
Adiponectin and SGA

- SGA has been correlated with the later occurrence of metabolic syndrome
- Adiponectin levels in previous SGA children?
- Although not all studies agree, most data support lower adiponectin levels in SGA children, especially in the subgroup of SGA with catch-up growth
  - *JCEM*, March 2004
Adiponectin levels in SGA children

Cianfarani et al, JCEM, March 2004
Adiponectin levels in SGA children

Cianfarani et al, JCEM, March 2004
In a recent study, among children born as SGA and examined at the age of 5, those who became overweight had lower adiponectin levels than SGA-born normal weight age-matched controls (12.9 mg/l vs 19.0 mg/l).

But....

- Not all studies come to the same conclusion
- Much more has to be written before final conclusions can be drawn...
- Therefore, here again, prevention is the best treatment
Endocrine Consequences of IUGR

- Metabolic syndrome
  - Cardiovascular disease
  - Hyperlipidemia
  - Diabetes mellitus type 2
  - Obesity

- On the reproductive axis
  - Premature adrenarche
  - PCOS
Premature adrenarche: 

- Definition 
Early increase in adrenal androgen production that usually results in the development of pubic hair or pubarche before the age of 8 yr in girls and 9 yr in boys
Precocious pubarche in SGA girls

Ibanez L et al, JCEM, 1998
Birthweight and reproductive axis dysfunction in girls

Ibanez L, JCEM, 1998
IUGR and PCOS

- **PCOS** = Polycystic ovarian Syndrome
- Is characterized by:
  - Menstrual irregularities
  - Obesity
  - Hyperandrogenemia
  - ↑ LH concentrations
  - U/S evidence of polycystic ovaries (in 50%)
PCOS

- Form of functional ovarian hyperandrogenism
- Hyperinsulinism and insulin resistance play a key role in ovarian growth and hyperandrogenism
IUGR

Insulin resistance

Premature adrenarche

PCOS

Reproductive axis dysfunction
IUGR and Reproductive Function

- According to the studies of F. De Zegher, L. Ibanez et al.
- Girls born as IUGR have higher incidence of premature adrenarche vs. Controls.
- Reduced numbers of primordial follicles.
- Anovulation in adolescence.
- Reduced uterus and ovarian size in adolescence.
## Low Birth Weight and Subsequent Male gonadal Function

<table>
<thead>
<tr>
<th></th>
<th>SGA group (n=25)</th>
<th>AGA group (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>17.5±1.3</td>
<td>17.6 ±2.0</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Testicular size (ml)</strong></td>
<td>16.3 ±2.7</td>
<td>22.8 ±3.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Testosterone (ng/ml)</strong></td>
<td>3.76 ±1.35</td>
<td>4.77 ±1.55</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>LH (IU/L)</strong></td>
<td>4.41 ±1.61</td>
<td>3.44 ±1.29</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>
Reduced fetal growth is associated with Dysfunction of the reproductive axis, expressed ,

I. in girls as

- Premature adrenarche
- PCOS, functional hyperandrogenism
- Reduced primordial follicles and uterus size

II. in boys, with lower testicular volume, and testosterone levels
IUGR and Postnatal Growth

- The vast majority of these newborns demonstrate catch-up growth, and these children are more at risk for the later development of metabolic syndrome.
- 8-12% of IUGR newborns do not demonstrate catch-up growth and may profit from the rhGH treatment.
IUGR and Cognitive Function

- Many studies have demonstrated the association between IUGR and:
  - Lower intelligence
  - Behavioral problems
  - Worse psychosocial functioning
- These findings are not consistent in all studies
Psychosocial functioning after rhGH in SGA

Van Pareren, JCEM, Nov. 2004
Psychosocial functioning after rhGH in SGA

Van Pareren, JCEM, Nov. 2004
Being Born As IUGR

- Means to be predisposed to many further morbidities
- Increased risk for metabolic syndrome
- Increased risk for reproductive axis dysfunction
- 8-12% probability to necessitate rhGH treatment
- Increased risk of impaired cognitive development
Conclusions (1)

- Every cause of IUGR may drive a re-programming of the endocrine-metabolic system of the fetus, with insulin resistance playing a key role.
- The reprogramming of the endocrine system may have long-life consequences, by inducing both metabolic syndrome and dysfunction of the reproductive axis.
Conclusions (2)

- In order to avoid the long-lasting economic and psychologic burden of both metabolic syndrome and reproductive dysfunction, we should pay special attention to *optimization of the intrauterine environment* by providing the ideal nutrient supply to the fetus and the ideal psychosocial support to the pregnant woman.