Programming of Renal Function before and after Birth

Jörg Dötsch
Perinatal Programming

Intrauterine milieu
  e.g. lack of energy, hypoxia

Postnatal phenotype i.e.
  SGA

Morbidity later in life
Perinatal Programming

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Persistent changes due to programming

Morbidity later in life
Birth weight and renal function (2,183,317 persons, born between 1967 and 2004 in Norway, 526 developed end stage renal failure)
Birth weight and renal function – Metaanalysis

Full review of 161 articles

131 excluded:
- No valid measure of kidney function
- Neonatal kidney function/failure
- Very low birth weight or very premature infants
- Outcome is renal cell cancer, Wilm’s Tumour, nephritis, nephrolithiasis, nephrocalcinosis
- Toxic exposure in utero
- Genetic studies/congenital abnormalities
- Studies of pathological subgroups

Unpublished data from 2 studies identified from other sources

32 studies eligible for inclusion
- Estimates of effect ascertained for 18 studies (17 cohort & case-control studies: n=46,249; 1 record linkage study: n = 2,183,317)
- 14 studies for which logistic regression estimates were unavailable (n = 3127)

(White et al., Am J Kidney Dis 2009)
Birth weight and kidney – Metaanalysis

(White et al., Am J Kidney Dis 2009)
Birth weight and renal function (Chronic Kidney Disease, DM or hypertension or first degree relative with DM or hypertension)  

N=2920

In white man inverse J-shape!  
In Afroamerican man J-shape!

(Li et al., Kidney Int 2008)
Birth weight and programming of renal function—questions
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SGA = IUGR?
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Causal relation IUGR – later morbidity?
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Prevention?
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Prevention?

Mechanisms of disease?
SGA = IUGR ?
SGA = IUGR ?

Weight

IUGR

Birth

Weeks of gestation

Weight

SGA

Birth

Weeks of gestation
IUGR always SGA?
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Causal relation?

Morbidity later in life
SGA: Glomerulosclerosis in childhood IgA-Nephropathy

(Zidar et al., Nephron 1998)
IUGR in rats (low protein model)

(Plank et al., Kidney Int., 2006)
IUGR + acute anti-Thy1.1-nephritis

Control

IUGR

NP-GN d4

LP-GN d4
IUGR + acute anti-Thy1.1-nephritis

Control

IUGR

NP-GN d4

LP-GN d4

NP-GN d14

(Plank et al., Kidney Int., 2006)
IUGR + acute anti-Thy1.1-nephritis

[Images showing histological sections labeled NP-GN d4, LP-GN d4, NP-GN d14, LP-GN d14, Control, IUGR]

(Plank et al., Kidney Int., 2006)
IUGR: Acute Anti-Thy1.1-Nephritis / day 14 Collagen (Immunohistochemistry)

A

glomerular Collagen I

Collagen I positive area per glomerular cross section (%)

NP d4  LP d4  NP d14  LP d14

IUGR +GN d27

(Plank et al., Kidney Int., 2006)
IUGR: Acute Anti-Thy1.1-Nephritis / day 14
Collagen (Immunohistochemistry)

A
glomerular Collagen I

Collagen I positive area per glomerular cross section (%)

<table>
<thead>
<tr>
<th></th>
<th>NP d4</th>
<th>LP d4</th>
<th>NP d14</th>
<th>LP d14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.2</td>
<td>3.3</td>
<td>5.6</td>
<td>6.1</td>
</tr>
</tbody>
</table>

* (*Plank et al., Kidney Int., 2006)*
Uterine artery ligation model: more severe course of anti-Thy1.1 Nephritis

(Nüsken et al., Endocrinology, 2008)
Uterine artery ligation model: more severe course of anti-Thy1.1 Nephritis

(SFB423 TP13
(Nüsken et al., Endocrinology., 2008)
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Transient Enalapril Application after IUGR before Anti-Thy1.1 Nephritis
Transient Enalapril Application after IUGR before Anti-Thy1.1 Nephritis

Manning and Vehaskari, Hypertension 2001
Transient Enalapril Application **after** IUGR **before** Anti-Thy1.1 Nephritis

![Graph showing systolic blood pressure over age (months) with IUGR and ACE-Inhibitor treatment](image)

Manning and Vehaskari, Hypertension 2001
Transient Enalapril Application after IUGR before Anti-Thy1.1 Nephritis

Collagen IV positive area per Glomerulum (%)

- **IUGR**
  - +Thy1
  - +Thy1 +Enal

- **Kontrolle**
  - +Thy1 +Enal

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Transient Enalapril Application after IUGR before Anti-Thy1.1 Nephritis

crescents /100 glomeruli

IUGR+THY1
IUGR+E+THY1
control+THY1
control+E+THY1

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Blood pressure after Hyperalimentation in SGA-patients (age of measurements 6-8 years)

<table>
<thead>
<tr>
<th></th>
<th>Standard (n = 83)</th>
<th>Nutrient Enriched (n = 70)</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic</td>
<td>61.3 (8.2)</td>
<td>64.5 (8.3)</td>
<td>-3.2</td>
<td>-5.8 to -0.5</td>
<td>0.02</td>
</tr>
<tr>
<td>MAP</td>
<td>76.9 (8.3)</td>
<td>79.5 (7.8)</td>
<td>-2.5</td>
<td>-5.1 to 0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic</td>
<td>100.5 (10.2)</td>
<td>102.2 (9.8)</td>
<td>-1.7</td>
<td>-4.9 to 1.5</td>
<td>0.3</td>
</tr>
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(Singal et al., Circulation, 2007)
Prevention of hyperalimentation after IUGR
Prevention of hyperalimentation after IUGR

Hyperalimentation

No hyperalimentation
Renal Inflammation after Prevention of Hyperalimentation (HA), day 70

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(Plank et al., submitted)
Glomerulosclerosis after Prevention of Hyperalimentation (HA), day 70

Glomerulosclerosis Score

HA-IUGR
HA-nonIUGR
non-HA-IUGR
non-HA-nonIUGR

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(Plank et al., submitted)
Albumine Excretion after Prevention of Hyperalimentation (HA), day 70, male animals

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(Plank et al., submitted)
Albumine Excretion after Prevention of Hyperalimentation (HA), day 360

(Boubred et al., Am J Physiol Renal Physiol, 2009)
Postnatal hyperalimentation only

Early postnatal period

- Gestation
- Birth
- Lactation
- Weaning
- Sacrifice, metabolic cage

16 – 18 animals (Co)
10 animals (WR10)
6 animals (WR6)
Outcome after postnatal hyperalimentation

body weight (g)

Coll I glomerular

Coll I interstitiell

SFB423 TP13
Outcome after postnatal hyperalimentation

body weight (g)

Coll I glomerular

Coll I interstitiiell
Outcome after postnatal hyperalimentation

**Albuminuria (g/g Crea (P120))**

![Box plot showing albuminuria](image)

**FeK**

![Bar chart showing FeK](image)

**MCP-1**

![Bar chart showing MCP-1 mRNA fold induction](image)

**PAI-1**

![Bar chart showing PAI-1 mRNA fold induction](image)

**IL-10**

![Bar chart showing IL-10 mRNA fold induction](image)
Role of NPY?

**IL-6 expression**

<table>
<thead>
<tr>
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<th>IL-6 mRNA fold induction</th>
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<tbody>
<tr>
<td>Co</td>
<td>0.0</td>
</tr>
<tr>
<td>WR10</td>
<td>2.5</td>
</tr>
<tr>
<td>WR6</td>
<td><strong>5.0</strong></td>
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**IL6/ßActin**

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Role of NPY?

IL-6 mRNA fold induction

IL-6 expression

IL-6/ß-Actin

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Role of NPY?

Release of IL-6 (into the supernatant)

IL-6 mRNA fold induction

IL-6 expression

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Role of NPY?

NPY expression

IL-6 expression

Release of IL-6 (into the supernatant)

NPY mRNA fold induction

IL-6 mRNA fold induction

IL-6/ßActin

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What Mechanisms?

Morbidity later in life
Nephrogenic zone in IUGR animals

Proliferating Cell Nuclear Antigen (PCNA)

Low protein model, P1
Nephron number after Prevention of Hyperalimentation (HA), day 70

glomeruli per kidney

HA-IUGR
HA-non-IUGR
nonHA-IUGR
nonHA-nonIUGR

*
**

(Plank et al., submitted)
Renin and $\text{AT}_{1b}$ after intrauterine growth restriction (Clear: control, black: IUGR)

(Bogdarina et al., Circ Res, 2007)
Methylation of AT1b-Promotor CpG-sites

(Bogdarina et al., Circ Res, 2007)
Placenta

Mother

Cortisol

Placenta

11β-HSD 2
Adequate placenta function

↓

Placenta-insufficiency

Gluco-/Mineralocorticoid Receptor

Fetus

Cortisol

Cortisol

Cortisol
11β-HSD 2
Adequate placenta function

11β-HSD 2 ↓
Placenta-insufficiency
11β-HSD 2 downregulated in IUGR placentae

(Struwe et al., Am. J. Obstet. Gynecol, 2007)
$11\beta$-HSD2 expression in placenta in relation to birth weight

$r = 0.58$
$p = 0.02$

(Tschoppe et al., Ped.Res., 2009)
$11\beta$-HSD2 Expression in Placenta is related to catch-up growth in IUGR-infants

(Tschoppe et al., Ped.Res., 2009)
Growth restriction

Placenta

Mother

Fetus

Cortisol

11β-HSD 2
Adequate placenta function

↓

Cortisol

- Growth restriction

- Modification of neuroendocrine development

Cortisol

11β-HSD 2 ↓
Placenta-insufficiency

Gluco-/ Mineralocorticoid Receptor
Growth restriction

Placenta function

Modification of neuroendocrine development

Postnatal change in cortisol metabolism
IUGR in rats: $11\beta$-HSD2 Gene Expression in Entire Kidney Tissue

(Bertam et al. Endocrinology, 2001)
IUGR in rats (low-protein): $11\beta$-HSD2
Immunohistochemistry and Gene Expression

(Östreicher et al., NDT in revision)
IUGR in rats (low-protein): 11β-HSD2
Immunohistochemistry and Gene Expression

(Östreicher et al., NDT in revision)
acetylcholine/flow-mediated

endothelial cell

BH4 ↓ → NOS ↓

vascular smooth muscle cell

ET-1 ↑

AT_{1b}-R ↑

α1 ↑

phenylephrine

NO ↓  →  O₂• ↑

cGMP ↓

Vasoconstriction ↑  Vasodilatation ↓
Renal endothelin-1 upregulation after intrauterine growth restriction

Relative Increase in renal Endothelin-1 Expression

Control

IUGR

p<0.001
Renal dysfunction

Renal Factors

- Epigenetic factors
- Reduced nephron number
- Increased activity of RAAS
- Reduced activity of 11β hydroxysteroid dehydrogenase

Extrarenal Factors

- Adverse intrauterine environment
- Epigenetic factors
- Pathological endothelial/smooth muscle function
- Sympathetic nerve activity
- Altered vascular structure

Epigenetic factors
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→ animal experiments (different models)
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→ animal experiments (different models)

Prevention?
→ avoiding hyperalimentation?
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Causal relation IUGR – later morbidity?
→ animal experiments (different models)

Prevention?
→ avoiding hyperalimentation?

Mechanisms?
→ extrarenal (e.g. endothelium, sympathetic nerve system)
→ renal (e.g. nephron number, RAAS, 11ß-HSD)
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