Fetal Programming

Impact of prenatal events on postnatal health

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www.medicinafetalbarcelona.org
Guillem was born at Maternitat (Hospital Clínic) with a diagnosis of mild fetal growth restriction. You even offered us to participate in a study of brain MRI.

Now he is almost 4 and he is suffering:
- Language disorders
- Motor delay
- Maturational delay
- Irritable mood with intolerance to frustration

Do you think these problems were caused by the problem of fetal growth restriction? Do you think this might cause further problems?

We remain awaiting your news,
BIOLIGIC PROGRAMMING AND AGE

IMPACT OF ENVIRONMENT

OPPORTUNITY FOR CORRECTION

Fetus  |  Child  |  Young  |  Mature  |  Old
Epigenetics:
- Changes in genetic function without changes in DNA sequence
- Induced by environment
- Transferrable to next generation

Alternative splicing

Methylation

Histone modifications / Chromatin conformation
Brain reorganization

Cardiovascular remodelling

Metabolic programming

Fetal growth restriction
(and other disorders associated with disease or abnormal environment)

Adaptation = Epigenetics = Permanent “programming”

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Dichorionic Twins. Born 34 weeks
Twin 1: 1950 g (p45)
Twin 2: 1200 g (p1). Normal Doppler

Bayley Score

- cognitive
- language
- motor
- socio-emotional
- adaptive behavior

Satchev, 2012
Figuera 2006-2011
Baschat 2009, 2011
Vohr 2004
Geva 2002-2011

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Fetal programming
Brain reorganization (+/- injury)

exposure
Neurocognitive disorders/Learning disabilities
Overall ≥10%
Estimated 2/3 of prenatal origin

Non-specific disorders
5-8%

Attention Deficit Hyperactivity Disorder
2-5%

Autism Spectrum Disorder
0.5-1%
Fetal growth restriction (and other disorders associated with disease or abnormal environment)

Adaptation = Epigenetics = Permanent “programming”
1986 Barker (MRC Unit, Southampton, UK):
Coronary heart disease mortality rates

Death rates from Coronary Heart Disease in men 1968-78
Infant Mortality 1901-1910

IMPACT OF FETAL GROWTH ON CARDIOVASCULAR REMODELLING

Normal growth

IUGR

BP 90/65

cIMT = 0.386 mm

BP 115/80

cIMT = 0.434 mm

www.medicinafetalbarcelona.org/  Crispi Circulation 2010
Shorter sarcomere length
Torre 2011, Iruretagoyena 2013

Protein expression and isoforms
Torre 2011, Tintu 2010

Sarcomeric intradistance of A-bands
Sarcomere length

Titin isoforms:
- N2BA compliant
- N2B stiffer
decreased systolic motion

![Graph showing decreased systolic motion]

- Right longitudinal systolic motion
- TAPSE

impaired relaxation

![Graph showing impaired relaxation]

- E dec
- IRT

Data are median + SEM. *P<0.05 adjusted by GA, birthweight centile and preeclampsia
Fetal growth restriction
(and other disorders associated with disease or abnormal environment)
Adaptation = Epigenetics = Permanent “programming”

Brain reorganization

Cardiovascular remodelling

Metabolic programming
4P medicine
- Predictive
- Preventive
- Personalized
- Participatory

Fetus

Child

Brain organization

Problem evident

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Neonatal and Fetal GA-adjusted “normal” weight in the same population
ISOLATED FETAL SMALLNESS = POORER PROGNOSIS
Perinatal and Long-term Outcomes

- Poor perinatal outcome + IUFD (Doppler) Signs of adaptation
  - IUGR
    - Placental insufficiency

- Perinatal outcome normal - No IUFD
  - SGA
    - Unknown (constitutional + others)

FGR vs. SGA: DIFFERENT MANAGEMENT
The discovery of UA and hemodynamics of IUGR

Constitutionally small  Placental insufficiency  Extrinsic cause

SGA  FGR  Primary fetal defect

FGR = abnormal UA Doppler

Savchev 2013
Prognostic criteria of “poor outcome” - SGA

CS for distress and/or neonatal acidosis

UtA >p95

CPR <p5

EFW CENTILE <3

N=447 SGA + 447 controls

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Late FGR vs. SGA

GA 34.4

Gender Male

EFW 1850

CPR 1.08

Uta PI 1.01

Centile\(^1\) 2

z-value\(^2\) -2.2

z-value\(^3\) 1.7

Late-IUGR

Follow up in 1 w

Repetir

2. Bocchat A Ultrasound Obstet Gynecol 2003
Distribution of cases when IUGR = abnormal UA Doppler

Savchev 2013

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Distribution of cases when IUGR = abnormal CPR or UtA or EFW < p3
fetal composite CV score for the prediction of postnatal hypertension
sensitivity 90%, specificity 77%

IDENTIFICATION OF RISK

INDIVIDUAL BIOMARKERS

INTERVENTION

WINDOW OF OPPORTUNITY

Fetus

Functional / structural organ remodeling

Problem evident

Cruz-Lemini FMF 2013, Skilton Pediatric 2012, Rodriguez 2013
La programación fetal determina una parte relevante de la salud postnatal

La principal causa de PF es el CIR, pero existen muchas otras causas (diabetes, HIV, exposición, TRA?...) y por determinar

La caracterización prenatal será una parte clave en la salud pública de la medicina (4P) del futuro
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IMPROVING DETECTION: THE DEFINITION OF “RESTRICTION”

Birthweight inverse relation with perinatal outcome AND brain-cardiac remodelling