Impact of (early and late) IUGR on neurodevelopment

Eduard Gratacos
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Hospitals Clinic and Sant Joan de Deu - University of Barcelona
www.fetalmedicinebarcelona.org
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1. IUGR vs. SGA - Early vs. Late

2. Early-onset IUGR and neurodevelopment

3. Late-onset IUGR and neurodevelopment
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The discovery of UA and hemodynamics of IUGR
The discovery of UA and hemodynamics of IUGR

Constitutionally small  Placental insufficiency  Extrinsic cause

Primary fetal defect

IUGR = abnormal UA Doppler
The discovery of UA and hemodynamics of IUGR

Constitutionally small → SGA
Placental insufficiency → IUGR
Extrinsic cause → IUGR = abnormal UA Doppler

Primary fetal defect

Savchev 2013
The discovery of UA and hemodynamics of IUGR

- Constitutionally small
- Placental insufficiency
- Extrinsic cause

Primary fetal defect

SGA
IUGR

IUGR = abnormal UA Doppler

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The discovery of UA and hemodynamics of IUGR

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SGA  IUGR

Primary fetal defect

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Savchev 2013

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Constitutionally small → SGA
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Savchev 2013

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The discovery of UA and hemodynamics of IUGR

- Constitutionally small: SGA
- Placental insufficiency: IUGR
- Extrinsic cause
- Primary fetal defect

IUGR = abnormal UA Doppler

![Graph showing UA Doppler + (EARLY-ONSET) cases]

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The discovery of UA and hemodynamics of IUGR

Constitutionally small
Placental insufficiency
Extrinsic cause

Primary fetal defect

SGA
IUGR

IUGR = abnormal UA Doppler

UA Doppler +
(EARLY-ONSET)

UA Doppler N
(LATE-ONSET)

N cases

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Distribution of cases when IUGR = abnormal UA Doppler

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Distribution of cases when IUGR = abnormal CPR or UtA or EFW

Savchev 2013

www.medicinafetalbarcelona.org/
IUGR = low CPR or high UtA or EFW < p3 or low PlGF
IUGR = low CPR or high UtA or EFW < p3 or low PI GF

www.fetalmedicinebarcelona.org/
IUGR= low CPR or high UtA or EFW<p3 or low PIGF

EARLY IUGR (1%)  LATE IUGR (5-7%)

32w @diagnosis

www.fetalmedicinebarcelona.org/
IUGR = low CPR or high UtA or EFW<p3 or low PI GF

<table>
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<tr>
<th>EARLY IUGR (1%)</th>
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<td>PROBLEM: MANAGEMENT</td>
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32w @diagnosis
IUGR = low CPR or high UtA or EFW < p3 or low PI GF

EARLY IUGR (1%)

PROBLEM: MANAGEMENT
Placental disease: high (UA+, PE high)

LATE IUGR (5-7%)

PROBLEM: DIAGNOSIS
Placental disease: low (UA-, PE low)
IUGR = low CPR or high UtA or EFW < p3 or low PlGF

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<td>Hypoxia ++: systemic CV adaptation</td>
<td>Hypoxia +/−: central CV adaptation</td>
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martes 18 de junio de 13
IUGR = low CPR or high UtA or EFW <p3 or low PlGF

EARLY IUGR (1%)

PROBLEM: MANAGEMENT
Placental disease: high (UA+, PE high)
Hypoxia ++: systemic CV adaptation
Tolerance to hypoxia. Natural history

LATE IUGR (5-7%)

PROBLEM: DIAGNOSIS
Placental disease: low (UA-, PE low)
Hypoxia +/-: central CV adaptation
Low tolerance: no natural history

www.fetalmedicinebarcelona.org/
IUGR = low CPR or high UtA or EFW < 3rd percentile or low PI GF

**EARLY IUGR (1%)**

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<td>High mortality and morbidity</td>
<td>Low mortality but poor long outcome.</td>
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**32w @diagnosis**
1. IUGR vs. SGA - Early vs. Late

2. Early-onset IUGR and neurodevelopment

3. Late-onset IUGR and neurodevelopment
early-IUGR is associated with higher frequency of ultrasound brain lesions and abnormal neonatal neurobehaviour

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<td>n (fetuses)</td>
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<td>GA at birth (wks)</td>
<td>31.2 (2.4)</td>
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<td>1078</td>
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Cruz et al. 2010

www.fetalmedicinebarcelona.org/
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Cruz et al. 2010

www.fetalmedicinebarcelona.org/
Early-onset IUGR
PREDICTION OF SERIOUS NEUROLOGICAL MORBIDITY

Perinatal Mortality

- <29: >90%
- 29-32: 30-40%
- >32.0: <10%

Fouron 2004
Del Rio 2008
Cruz-Martinez 2012

www.fetalmedicinebarcelona.org/
Early-onset IUGR

PREDICTION OF SERIOUS NEUROLOGICAL MORBIDITY

Brain US anomalies in 30w IUGR

- Controls
- IUGR antegrade AoI
- IUGR retrograde AoI

Perinatal Mortality

- >90%
- 30-40%
- <10%

Fouron 2004
Del Rio 2008
Cruz-Martinez 2012

www.fetalmedicinebarcelona.org/
Early-onset IUGR: TARGETED NEUROSONOGRAPHY

Abnormal findings = 16% (n=108)

Eixarch 2013
SEVERE IUGR: TARGETED NEUROSONOGRAPHY
Early-onset IUGR has a strong association with poor short-term and long-term adverse neurological outcome

Early-onset IUGR: Indication for neurosonography

If NSG normal: strongest predictor is GA<30w
Best predictor aside of GA: aortic isthmus (32-37w)
1. IUGR vs. SGA - Early vs. Late

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exposure
Fetal programming
Brain reorganization (+/- injury)

exposure
Altered small-world topology of structural brain networks in infants with intrauterine growth restriction and its association with later neurodevelopmental outcome

Dafnis Batalle, Eleniida Eixarch, Francesc Figueras, Emma Muñoz-Moreno, Nuria Bargallo, Miriam Ilia, Ruthy Acosta-Rojas, Ivan Amlat-Roldan, Eduard Gratacos

Batalle 2012
Eixarch 2012
Altered small-world topology of structural brain networks in infants with intrauterine growth restriction and its association with later neurodevelopmental outcome

Dafnis Batalle, Eleonora Eixarch, Francesc Figueras, Emma Muñoz-Moreno, Nuria Bargallo, Miriam Ilià, Ruthy Acosta-Rojas, Ivan Arnaut-Roldán, Eduard Giraltes

Batalle 2012
Eixarch 2012
Dichorionic Twins. Born 34 weeks
Twin 1: 1950 g (p45)
Twin 2: 1200 g (p1). Normal Doppler
Dichorionic Twins. Born 34 weeks
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Bayley Score

Bayley Score

satchev, 2012
figueras 2006-2011
baschat 2009, 2011
vohr 2004
geva 2002-2011
marsal 00-06
visser 01-11
Dichorionic Twins. Born 34 weeks
Twin 1: 1950 g (p45)
Twin 2: 1200 g (p1). Normal Doppler

Lagercrantz H. Better born too soon than too small.
Lancet 1997
Clinical implications:

Does delivery at 37 weeks improve outcomes?

Does SGA vs IUGR affect prognosis?

Prediction with biomarkers
Effects on (neuro)developmental and behavioral outcome at 2 years of age
Induced labor vs. expectant management in late SGA (EFW<10th centile)
(DIGITAT trial) AJOG 2012

292 24-months SGA ≥37 weeks
Neurobehavioral performance of term SGA vs IUGR

Bayley’s scores at 2 years
No differences in relation with IUGR or SGA status (EFW<3, CPR or UtA Doppler)
Bayley’s scores at 2 years

No differences in relation with IUGR or SGA status ($EFW < p3, CPR$ or $UtA$ Doppler)

Cortical measures

Egaña 2013
Brain cortical development in patients with high risk of abnormal neurodevelopment (IUGR)

Egaña 2013
Brain cortical development in patients with high risk of abnormal neurodevelopment (IUGR)

Integrated algorithm with several brain CD measures

Composite score = $e^{-Y} / \left(1 + e^{-Y}\right)$,
where $Y = 6.259 + \left[\left(LID/BPD \times RID/BPD \times -41.264\right) + \left(LPOD/BPD \times -16.247\right)\right]$. 

Egaña 2013
BIOLOGIC PROGRAMMING AND AGE

Early and Late-Onset IUGR
BIOLOGIC PROGRAMMING AND AGE
Early and Late-Onset IUGR

IMPACT OF ENVIRONMENT

OPPORTUNITY FOR CORRECTION

Fetus  Child  Young  Mature  Old
Fetus

Brain organization

Problem evident

Child

WINDOW OF OPPORTUNITY

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IDENTIFICATION OF RISK

INDIVIDUAL BIOMARKERS

INTERVENTION

WINDOW OF OPPORTUNITY

Fetus

Brain organization

Child

Problem evident

CLÍNIC
Hospital Universitari

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IDENTIFICATION OF RISK

INDIVIDUAL BIOMARKERS

INTERVENTION

WINDOW OF OPPORTUNITY

BIRTH

Fetus

Child

Brain organization

Problem evident

Fetus

Child

Genes

(Early) postnatal

Fetal

Intelligence

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Being small for gestational age has a strong association with poor long-term adverse neurological outcome regardless of the cause.

Detection of smallness is an opportunity to improve long-term health outcomes and ageing.

Individualized prediction of risk will likely be possibly but not applicable as public health.