UPDATE ON DIAGNOSIS AND MANAGEMENT OF FETAL GROWTH RESTRICTION

Eduard Gratacós

BCNatal – Barcelona Center of Maternal-Fetal and Neonatal Medicine
Hospital Clínic and Hospital Sant Joan de Déu, Universitat de Barcelona

www.fetalmedicinebarcelona.org/
Placental insufficiency = high risk of IUFD and fetal/neonatal acidosis
Fetal Smallness = higher risk of placental insufficiency

Risk of placental insufficiency

Fetal weight centile

Non-“respiratory” smallness = no distress/IUFD risk

Placental “respiratory” smallness = risk distress + IUFD

“Small fetuses”
1. Identify small fetus

2. Identify placental insufficiency (FGR vs. SGA)

3. Determine timing of delivery
Neonatal and Fetal GA-adjusted “normal” weight in the same population
IMPROVING DETECTION: THE DEFINITION OF “RESTRICTION”

Birthweight inverse relation with perinatal outcome AND brain-cardiac remodelling
1. Identify small fetus

2. Identify placental insufficiency (FGR vs. SGA)

3. Determine timing of delivery
Excluding primary fetal defect

Excluding extrinsic cause

**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
  
  NO signs of adaptation

**SGA**

Unknown (constitutional + others)

FGR vs. SGA: DIFFERENT MANAGEMENT
Constitutionally small  Placental insufficiency  Extrinsic cause

SGA  FGR

Primary fetal defect

FGR = abnormal UA Doppler

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FGR = abnormal UA Doppler?

UA Doppler + (EARLY-ONSET)

UA Doppler N (LATE-ONSET)

Savchev 2013

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Prognostic criteria for poor outcome among small fetuses with normal UA Doppler

- CPR <p5
- UtA >p95
- EFW CENTILE <3

**Risk of CS for distress and/or neonatal acidosis**

*N* = 509 SGA + 509 controls

- Controls: 8%
- All normal: 11%
- Any abnormal: 40%

Figueras 2012

[www.fetalmedicinebarcelona.org/](http://www.fetalmedicinebarcelona.org/)
FGR = EFW <p10 + any of

- CPR <p5
- UtA >p95
- EFW CENTILE <3
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

Savchev 2013

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ISOLATED FETAL SMALLNESS = POORER PROGNOSIS
Perinatal and Long-term Outcomes

- Poor perinatal outcome + IUFD (Doppler) Signs of adaptation
- Perinatal outcome normal - No IUFD
  NO signs of adaptation

**IUGR**
Placental insufficiency

**SGA**
Unknown (constitutional + others)

FGR vs. SGA: DIFFERENT MANAGEMENT
1. Identify small fetus

2. Identify placental insufficiency (FGR vs. SGA)

3. Determine timing of delivery
IUGR = abnormal CPR or UtA or EFW < p3

Savchev 2013

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IUGR = abnormal CPR or UtA or EFW<p3
Management = when should we deliver?

Early-severe
High risk IUFD preterm

Late-mild
Low risk IUFD (high at term)
RATIONALE FOR AN INTEGRATED STAGE-BASED APPROACH TO THE MANAGEMENT OF FGR

PLACENTAL DISEASE

<table>
<thead>
<tr>
<th>Stage fetal deterioration</th>
<th>Risks of prematurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>MINIMAL</td>
</tr>
<tr>
<td>II</td>
<td>MILD</td>
</tr>
<tr>
<td>III</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

HYPOXIA

Diagnostic/chronic markers
DIFFERENCE
FGR VS SGA

Increment placental impedance

ACIDOSIS

Prognostic/Acute markers
INDICATION ABOUT THE SHORT-TERM RISK
OF IUFD/BRAIN INJURY

SERIOUS INJURY

DEATH

Cardiac ischemia

Diastolic failure

Systolic cardiac failure

Centralization

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Protocol IUGR
First step: UtA + CPR + EFW = SGA or IUGR

I  low EFW (<p3) or mild placental resistance / redistribution

II  Severe placental resistance / redistribution

III Severe hemodynamic adaptation - Low suspicion acidosis

IV  High suspicion of acidosis - High risk of death

CPR <p5  Ut A >p95  MCA <p5
AEDV  Aol >p95
DV >p95  REDV

DV (a rev)
CGT decelerations of reduced short-term variability

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IUGR

Management protocol according to severity stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;26w</th>
<th>26-28</th>
<th>28-30</th>
<th>30-34</th>
<th>34-37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mort.</td>
<td>&gt;90%</td>
<td>50%</td>
<td>&lt;10%</td>
<td>50%</td>
<td>LOW</td>
</tr>
<tr>
<td>Morb.</td>
<td>&gt;90%</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of IUFD/brain injury</td>
<td>LOW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deliver at</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/w</td>
</tr>
<tr>
<td>Mode</td>
<td></td>
<td></td>
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<td>LI</td>
</tr>
</tbody>
</table>

EFW<p3, CPR <p5, UtA>95

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UA Doppler PI: 1.26 Percentile: 70

UA Diastolic flow: Present

MCA Doppler M.CA PI:
1.15

Ut.A Right Doppler:
1.4

Ut.A Left Doppler:
1.1

CPR (Percentile:1)
0.91

Ao Isthmus Diastolic Flow:
Present

DV PI: 0.91 Percentile: 50

D.V. Atrial Flow:
Present

Fetal Growth restriction:
Stage 1
Recommended management:
Follow-up in 1 week

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Stage 1

Recommended management: Delivery
First goal:
Identify of small fetus (EFW<\text{p10}) and classify as FGR vs SGA according to CPR, UtA and EFW<3.

Second goal:
Decide timing of delivery and followup scheme: use a stage-based integrated protocol.
Early vs. Late onset IUGR
EARLY-ONSET

LATE-ONSET

PREECLAMPSIA

PREECLAMPSIA + IUGR

IUGR

1 %

1 %

4-8 %

4-8 %

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

<table>
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<th>PROBLEM: MANAGEMENT</th>
<th>PROBLEM: DIAGNOSIS</th>
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<tr>
<td>Placental disease: high (UA+, PE high)</td>
<td>Placental disease: low (UA-, PE low)</td>
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<tr>
<td>Hypoxia ++: systemic CV adaptation</td>
<td>Hypoxia +/-: central CV adaptation</td>
</tr>
<tr>
<td>Tolerance to hypoxia. Natural history</td>
<td>Low tolerance: no natural history</td>
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<tr>
<td>High mortality and morbidity</td>
<td>Low mortality but poor long outcome.</td>
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FETAL DETERIORATION IN PLACENTAL INSUFFICIENCY

PLACENTAL DISEASE
- Increment placental impedance
- UTERINE A. >p95
- Centralization
- MIDDLE CEREBRAL A. <p5
- Ao ISTHMUS >p95
- CPR <p5
- UMBILICAL A. >p95

COMPENSATED HYPOXIA
- growth

DECOMPENSATED HYPOXIA
- cardiac ischemia
- Diastolic failure
- DUCTUS VENOSUS >p95 and a-
- cCTG: reduced short-term variability

SERIOUS INJURY DEATH
- CTG ABNORMAL
- Systolic cardiac failure

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FETAL DETERIORATION IN PLACENTAL INSUFFICIENCY
EARLY VS LATE IUGR (>34s)

PLACENTAL DISEASE

INCREMENT PLACENTAL IMPEDANCE

COMPENSATED HYPOXIA

MINIMAL TOLERANCE TO HYPOXIA

DECOMPENSATED HYPOXIA

PLACENTAL INJURY <30%

UTERINE A. >p95

CPR <p5

UMBILICAL A. >p95

CENTRALIZATION

MIDDLE CEREBRAL A. <p5

Ao ISTHMUS >p95

cardiac ischemia
Diastolic failure

DUCTUS VENOSUS >p95 and a-

CTG / BPP ABNORMAL

Systolic cardiac failure

growth

mild hypoxia
no cardiovascular adaptation

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

<table>
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<th>EARLY IUGR (1-2%)</th>
<th>LATE IUGR (5-6%)</th>
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Parameters for fetal follow up in IUGR
umbilical artery
normal and anormal hemodynamics

Cardiac pump
normal function

Cardiac pump
abnormal function

Placental status

<30%

placenta + cardiac ischemia

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middle cerebral artery
normal and abnormal hemodynamics

Normal oxygenation

[normal waveform]

[mild vasodilation]

[marked vasodilation]

hypoxia
Cerebroplacental ratio is more sensitive than UA or MCA alone

IPUA=p80 + IPMCA=p20 = CPR <p5

Sensitivity (95% CI)
- Bahado-Singh RO: 0.41 (0.30 - 0.52)
- Obido AO: 0.61 (0.49 - 0.72)
- Arias F: 0.49 (0.32 - 0.65)
- Gramellini D: 0.86 (0.42 - 1.00)
- Makhseed M: 0.63 (0.42 - 0.81)
- Habek D: 0.39 (0.17 - 0.64)
- Sterne G: 0.58 (0.39 - 0.75)
- Yalti S: 0.86 (0.57 - 0.98)
- Ebrashy A: 1.00 (0.89 - 1.00)

Pooled Sensitivity = 0.59 (0.53 to 0.64)
Chi-square = 57.86, df = 8 (p = 0.0000)
Inconsistency (I-square) = 86.2%
30% venous return

REFLECTS DIASTOLIC PRESSURE IN RIGHT (AND LEFT) HEART

www.fetalmedicinebarcelona.org/
ductus venosus
normal and abnormal hemodynamics

Venous vessel: pulsation due to retrograde pressure
ductus venosus
normal and abnormal hemodynamics

compliance right chambers: effect sobre on venous return

no Myocardial ischemia

compliance
IFI

VTI sistole + VTI diástole
VTI sistole

Fouron AJOG 2001, Del Rio UOG 2006
When and how to deliver
IUGR = abnormal CPR or UtA or EFW<p3

Management = when should we deliver?

Early-severe
High risk IUFD preterm

Late-mild
Low risk IUFD (high at term)

PROTOCOL

Stage II to IV
Stage I
>37w
Early-onset IUGR

PROBLEM #1: MORTALITY

Pathological CGT

DVa (rev)

Perinatal Mortality

<26
>90%

26-28
30-40%

29-30
<10%

31-34

BPP

IUFD 23% in BPP=6 and 11% in BPP=8
Poor correlation with DVa(rev)
Cochrane: poor contribution to prediction
Baschat 2007, Kafur 2008, Lalor 2010,

www.fetalmedicinebarcelona.org/
Early-onset IUGR

PROBLEM #2: (NEUROLOGICAL) MORBIDITY

Neonatal brain US anomalies in 30-34w IUGR

Controls  IUGR ant AoI  IUGR REV AoI

<29  29-32  >32.0

Neurological Morbidity

>90%  30-40%  <10%

Fouron 2004
Del Rio 2008
Cruz-Martinez 2012

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Late-onset IUGR
PROBLEM #1: WHEN AND HOW TO DELIVER

37-38 w (+/- check lung maturity)
Do not use prostaglandins (Foley/Balloon)
Select high risk cases (MCA Doppler)
Cesarean section for fetal distress after labor induction in term SGA according to MCA Doppler (N=202)

(OVERALL RISK OF CS AFTER INDUCTION 80 %)

Cruz et al, 2010

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RISK RESPIRATORY MORBIDITY

![Bar chart showing the risk of respiratory distress syndrome (%) by gestational age (weeks). The risk decreases as gestational age increases, with the highest risk at 30 weeks (59.1%) and the lowest risk at 40 weeks (1.2%).](www.fetalmedicinebarcelona.org/)
• N=144
• Singleton
  pregnancies
• 29.0 - 38.6 w
• Axial thoracic
  section

Bonet, UOG 2014

Neonatal Respiratory
Morbidity (*):
• Respiratory Distress
  Syndrome
• Transient tachypnea of
  newborn

(*) RDS: Respiratory symptoms (eg, grunting, flaring, tachypnea, retractions), O2 requirement + chest
Rx + NICU admission
TT: chest Rx impression + clinical
diagnosis by clinician in charge.
JAMA 2010
**Performance of Quantus FLM and comparison with currently used lab**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/S Ratio</td>
<td>72%</td>
<td>84%</td>
<td>37%</td>
<td>95%</td>
</tr>
<tr>
<td>PG</td>
<td>88%</td>
<td>65%</td>
<td>24%</td>
<td>97%</td>
</tr>
<tr>
<td>Lamellar body</td>
<td>88%</td>
<td>66%</td>
<td>19%</td>
<td>98%</td>
</tr>
<tr>
<td>QuantusFLM(^8)</td>
<td><strong>86%</strong></td>
<td><strong>86%</strong></td>
<td><strong>62%</strong></td>
<td><strong>96%</strong></td>
</tr>
</tbody>
</table>

\(^8\)QuantusFLM\(^8\) ha sido validado mediante 144 muestras ciegas.
Late IUGR with MCA<p5
Planned delivery at 37.0 weeks

RISK RESPIRATORY MORBIDITY

BASELINE GA-ADJUSTED = 4%

PERSONALIZED: FETAL LUNG MATURITY

LOW RISK = 1.5%

Deliver

HIGH RISK = 25%

Wait and follow-up until 37.6-38.0

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Early and late-onset determines different severity, fetal response and natural history.

Doppler is the main tool for follow-up and timing of delivery in stage II to IV.

Stage I: challenge is to determine best timing and mode of delivery.
BEING SMALL EARLY IN PREGNANCY IS A PROBLEM

PROBLEM #1: MORTALITY

Perinatal Mortality

- <26: >90%
- 26-28: 30-40%
- >28: <10%

Pathological CGT

- DVa (rev)
  - Yes: 19%
  - No: 60%

- cCTG-STV<3 ms

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Baschat 2003
Hecher 2003
Grivell 2009
Cruz-Lemini 2012
Early-onset IUGR

PROBLEM #2: (NEUROLOGICAL) MORBIDITY

Neonatal brain US anomalies in 30-34w IUGR

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Neurological Morbidity

>90%  30-40%  <10%

Fouron 2004
Del Rio 2008
Cruz-Martinez 2012

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BEING SMALL LATE IS ALSO A PROBLEM

SGA

Significant increase in the risk of adverse perinatal outcome

Hershkovitz et al. Ultrasound Obstet Gynecol 2000
Severi et al. Ultrasound Obstet Gynecol 2002

Significant increase in the risk of adverse neurodevelopment

Eixarch et al. Ultrasound Obstet Gynecol 2008
Severi et al. Ultrasound Obstet Gynecol 2002

SGA = constitutionally small?

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SGA: proportion of perinatal adverse outcomes in 376 consecutive cases

- Neonatal acidosis: 5%
- CS for distress: 15%
- Abnormal NBAS: 30%
- Any: 40%
Classification of stillbirth by relevant condition at birth (ReCoDe): population-based cohort study
Gardosi et al. BMJ 2005 and 2013

IUGR as relevant condition identified in 43-60%

Overall stillbirth rate (/ 1000 births) 4.2, but only 2.4 in non-SGA pregnancies, increasing to 9.7 with antenatally detected IUGR and 19.8 in not detected IUGR.
Neurobehavioral performance of term SGA newborns

N=120
SGA vs 100 AGA

* p <0.05
Adjusted for GA, maternal age, socioeconomic status and smoking

Bayley Score

cognitive  language  motor  socio-emotional  adaptive behavior

Satchev, 2012
Geva 2008
Figueras 2008
Eixarch 2010

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Cardiovascular programming in SGA / late-IUGR

Fetuses EFW<p10 evaluated at 5 years

*Classified by CPR, p3 and UtA Doppler:*
- All normal: SGA
- Any abnormal: late-IUGR

Crispi 2010

[Images of control and IUGR fetuses]

[Graph showing sphericity index: globular hearts]