UPDATE ON DIAGNOSIS AND MANAGEMENT OF FETAL GROWTH RESTRICTION

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www.fetalmedicinebarcelona.org/
1. Identify small fetus

2. FGR vs. SGA

3. Early vs. Late

4. Parameters for fetal follow-up

5. Stage-based management protocol
Detect SGA fetuses

1st: Accurate dating

2nd: Accurate measuring
US Dating

<14.0 w:  CRL  (Robinson)  

14-24 w:  BPD  (Mul)  

>24 w:  HC±LFL  (Snijders)

n=3450 (spontaneous deliveries)

## US Dating

**Review:** Ultrasound for fetal assessment in early pregnancy  
**Comparison:** 1 Routine/revealed versus selective/concealed ultrasound in early pregnancy  
**Outcome:** 31 Induction of labour for any reason

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Routine scan n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alesund</td>
<td>34/774</td>
<td>77/750</td>
<td></td>
<td>11.8%</td>
<td>0.43 [0.29, 0.63]</td>
</tr>
<tr>
<td>London 1982</td>
<td>104/531</td>
<td>107/531</td>
<td></td>
<td>15.5%</td>
<td>0.97 [0.76, 1.24]</td>
</tr>
<tr>
<td>Missouri 1990</td>
<td>91/402</td>
<td>103/413</td>
<td></td>
<td>15.4%</td>
<td>0.91 [0.71, 1.16]</td>
</tr>
<tr>
<td>Oxford 2006</td>
<td>34/233</td>
<td>46/230</td>
<td></td>
<td>11.5%</td>
<td>0.73 [0.49, 1.09]</td>
</tr>
<tr>
<td>RADIUS</td>
<td>1912/7617</td>
<td>1858/7534</td>
<td></td>
<td>19.1%</td>
<td>1.02 [0.96, 1.08]</td>
</tr>
<tr>
<td>Sweden</td>
<td>140/2389</td>
<td>218/2412</td>
<td></td>
<td>16.4%</td>
<td>0.65 [0.53, 0.80]</td>
</tr>
<tr>
<td>Trondheim 1984</td>
<td>32/496</td>
<td>38/478</td>
<td></td>
<td>10.4%</td>
<td>0.81 [0.52, 1.28]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
12442 / 12348  

Total events: 2347 (Routine scan), 2447 (Control)  
Heterogeneity: Tau² = 0.06; Chi² = 37.57, df = 6 (P<0.00001); I² = 84%  
Test for overall effect: Z = 2.24 (P = 0.025)

[www.medicinafetalbarcelona.org/](http://www.medicinafetalbarcelona.org/)
Detect SGA fetuses

1st: Accurate dating

2nd: Accurate measuring
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. FGR vs. SGA

3. Early vs. Late

4. Stage-based management protocol
Exclude primary fetal defect

Exclude extrinsic cause

Isolated Fetal Smallness = Poorer Prognosis

Perinatal and Long-term Outcomes

<table>
<thead>
<tr>
<th>Poor perinatal outcome + IUFD</th>
<th>Perinatal outcome normal - No IUFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Doppler) Signs of adaptation</td>
<td>NO signs of adaptation</td>
</tr>
</tbody>
</table>

IUGR  
Placental insufficiency

SGA  
Unknown (constitutional + others)

FGR vs. SGA: Different Management

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The discovery of UA and hemodynamics of IUGR

Constitutionally small → SGA
Placental insufficiency → FGR
Extrinsic cause → Primary fetal defect

FGR = abnormal UA Doppler

Savchev 2013

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BEING SMALL EARLY IN PREGNANCY IS A PROBLEM

PROBLEM #1: MORTALITY

Perinatal Mortality

<26  26-28  >28

>90%  30-40%  <10%

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

PROBLEM #2: (NEUROLOGICAL) MORBIDITY

Brain US anomalies in 30w IUGR

- Controls
- IUGR ant AoI
- IUGR REV AoI

Neurological Morbidity

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

Fouron 2004
Del Rio 2008
Cruz-Martinez 2012

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BEING SMALL LATE IS ALSO A PROBLEM

SGA = constitutionally small?

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: proportion of perinatal adverse outcomes in 376 consecutive cases

- Neonatal acidosis
- CS for distress
- Abnormal NBAS
- Any

Figueras 2011
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

- Attention
- Habitation
- Motor
- Social-interactive
- State regulation

- Cognitive
- Language
- Motor
- Socio-emotional
- Adaptive behavior

Satchev, 2012
Geva 2008
Figueras 2008
Eixarch 2010
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
FGR = abnormal UA Doppler?

UA Doppler + (EARLY-ONSET)

UA Doppler N (LATE-ONSET)

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Prognostic criteria of “poor outcome”-SGA

CS for distress and/or neonatal acidosis

UtA >p95

CPR <p5

EFW CENTILE <3

N=509 SGA + 509 controls

Figueras 2012
Late-onset intrauterine growth restriction vs. small-for-gestational age (submitted)

40% of late-SGA with 11% risk (14% of all adverse outcomes)

60% of late-SGA with 40% risk (86% of all adverse outcomes)

Figueras 2012
FGR = EFW <p10 + any of

- UtA >p95
- CPR <p5
- EFW CENTILE <3
Distribution of cases when IUGR = abnormal UA Doppler

Savchev 2013
Distribution of cases when IUGR = abnormal CPR or UtA or EFW < p3

Savchev 2013

www.medicinafetalbarcelona.org/
Exclude primary fetal defect

Exclude 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
1. Identify small fetus

2. FGR vs. SGA

3. Early vs. Late

4. Stage-based management protocol
EARLY-ONSET

LATE-ONSET

1 %

PREECLAMPSIA

PREECLAMPSIA + IUGR

IUGR

4-8 %

4-8 %

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

### Table: Early IUGR (1%) vs Late IUGR (5-7%)

<table>
<thead>
<tr>
<th>Early IUGR (1%)</th>
<th>Late IUGR (5-7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem: Management</strong></td>
<td><strong>Problem: Diagnosis</strong></td>
</tr>
<tr>
<td>Placental disease: high (UA+, PE high)</td>
<td>Placental disease: low (UA-, PE low)</td>
</tr>
<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>
</tr>
<tr>
<td>High mortality and morbidity</td>
<td>Low mortality but poor long outcome.</td>
</tr>
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Diagram showing the progression of IUGR and SGA from 20 weeks to 40 weeks, with a peak at 32 weeks @ diagnosis.
FETAL DETERIORATION IN PLACENTAL INSUFFICIENCY

PLACENTAL DISEASE

- Increment placental impedance

COMPENSATED HYPOXIA

- UTERINE A. >p95
- CPR <p5
- UMBILICAL A. >p95
- Centralization
- MIDDLE CEREBRAL A. <p5
- Ao ISTHMUS >p95
- growth

DECOMPENSATED HYPOXIA

- cardiac ischemia
- Diastolic failure
- DUCTUS VENOSUS >p95 and a-

SERIOUS INJURY

- DEATH
- CTG ABNORMAL
- cCTG: reduced short-term variability
- Systolic cardiac failure

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

PLACENTAL DISEASE

INCMENT placental impedance

UTERINE A. >p95

CPR <p5

UMBILICAL A. >p95

Centralization

MIDDLE CEREBRAL A. <p5

Ao ISTMUS >p95

COMPENSATED HYPOXIA

minimal tolerance to hypoxia

Placental injury <30%

growth

mild hypoxia
no cardiovascular adaptation

DECOMPENSATED HYPOXIA

cardiac ischemia
Diastolic failure

DUCTUS VENOSUS >p95 and a-

Systolic cardiac failure

SERIOUS INJURY
DEATH

CTG / BPP ABNORMAL

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### CLINICAL PROBLEMS

#### # 1: DIAGNOSIS
detection <50%

#### # 2: POOR PERINATAL OUTCOME (~50%)
- A “Late-IUGR subset” with poorer perinatal outcome can be identified

#### # 3: LONG TERM OUTCOME (~50%)
Fetal programming

- 5-7% newborns
- detection < 50%
- > 40% late pregnancy IUFD
- Neurological, cardiovascular and metabolic impact
- diagnosis SGA vs. Late-IUGR

[Diagram]

Signs adaptation/severity:
- yes
- poorer

Perinatal outcome:
- no
- normal

Percentage: 0-3

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

<table>
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<th>EARLY IUGR (1%)</th>
<th>LATE IUGR (5-7%)</th>
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<td>PROBLEM: MANAGEMENT</td>
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1. Identify small fetus

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3. Early vs. Late

4. Parameters for fetal follow up

4. Stage-based management protocol
umbilical artery
normal and anormal hemodynamics

Cardiac pump
normal function

<30%
placenta + cardiac ischemia

Placental status

Cardiac pump
abnormal function
middle cerebral artery
normal and abnormal hemodynamics

Normal oxygenation
[normal waveform]

[mild vasodilation]

[marked vasodilation]

hypoxia
30 % venous return
REFLECTS DIASTOLIC PRESSURE IN RIGHT (AND LEFT) HEART
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

Myocardial ischemia
IFI

VTI sístole + VTI diástole
VTI sístole

Fouron AJOG 2001, Del Río UOG 2006
Early-onset IUGR

PROBLEM #1: MORTALITY

Perinatal Mortality

<26
>90%

26-28
30-40%

>28
<10%

Pathological CGT

DVa (rev)

BPP

IUFD 23% in BPP=6 and 11% in BPP=8
Poor correlation with DVa(rev)
Cochrane: poor contribution to prediction

www.medicinafetalbarcelona.org/
Early-onset IUGR

PROBLEM #2: (NEUROLOGICAL) MORBIDITY

Brain US anomalies in 30w IUGR

- Controls
- IUGR antegrade AoI
- IUGR retrograde AoI

Perinatal Mortality

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

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Fouron 2004
Del Rio 2008
Cruz-Martinez 2012
1. Identify small fetus

2. FGR vs. SGA

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4. Parameters for fetal follow up

5. Stage-based management protocol
IUGR = abnormal CPR or UtA or EFW<p3

Savchev 2013
RATIONALE FOR A STAGE-BASED APPROACH TO THE MANAGEMENT OF FGR

PLACENTAL DISEASE
- Diagnostic/chronic markers
  - Early and Late IUGR
  - Increment placental impedance
- Prognostic/Acute markers
  - Early IUGR

HYPOXIA
- Centralization
- cCTG: reduced STV

ACIDOSIS
- Systolic cardiac failure

SERIOUS INJURY
- Diastolic failure

DEATH
- cardiac Diastol
- Systolic cardiac failure

Risks of prematurity
- Stage fetal deterioration
- LOW
- MODERATE
- HIGH

Red Line LATE IUGR
Red Line EARLY IUGR

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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  UtA >p95  MCA <p5

AEDV  Aol >p95

DV >p95  REDV

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

www.medicinapetalbarcelona.org/
## IUGR

### Management protocol according to severity stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Delivery</th>
<th>Follow-up</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26w</td>
<td>DV&gt;p95</td>
<td>CS</td>
<td>1/w</td>
<td>Li</td>
</tr>
<tr>
<td>26-28</td>
<td>REDV</td>
<td>CS or LI</td>
<td>2/w</td>
<td></td>
</tr>
<tr>
<td>28-30</td>
<td>(a) AEDV</td>
<td>LI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>(b) AoI&gt;95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34-37</td>
<td>EFW&lt;p3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPR&lt;p5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UtA&gt;p95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCA&lt;p5</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mort.</th>
<th>Morb.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>50%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Late FGR vs. SGA

GA 34.4

Gender: Male

EFW 1950

CPR 1.85

UtA PI 0.85

Centile\(^1\): 4

\( z\)-value\(^2\): -0.6

\( z\)-value\(^3\): 0.9

SGA

Follow up in 2 w

Repetir

References:
2. Baschat A Ultrasound Obstet Gynecol 2003
Late FGR vs. SGA

GA: 34 weeks 4 days

EFW: 1850

Gender: Male

UA PI: 1.25

MCA PI: 1.35

UtA PI: 1.01

Calculate
Late FGR vs. SGA

GA  34.4

Gender  Male

EFW  1850

CPR  1.08

UtA PI  1.01

Centile¹  2
z-value²  -2.2
z-value³  1.7

Late-IUGR
Follow up in 1 w

2. Baschat A Ultrasound Obstet Gynecol 2003

Repetir
**UA Doppler PI:**
1.26   Percentile: 70

**UA Diastolic flow:**
Present

**MCA Doppler PI:**
1.15

**Ut.A Right Doppler:**
1.4

**Ut.A Left Doppler:**
1.1

**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

www.fetalmedicinebarcelona.org/
Stage 1
Delivery

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

Ao Isthmus Diastolic Flow: Present

DV PI: 0.91  Percentile: 50

D.V. Atrial Flow: Present

CPR (Percentile:1) 0.91

Fetal Growth restriction:

www.fetalmedicinebarcelona.org/
The main goal in FGR is identification

Small fetus (EFW < p10) must be divided in:
- FGR (placenta, poor perinatal and long-term outcome)
- SGA (we don’t know, perinatal outcome N, poor long term)

Early and late-onset FGR (GA 32s) represent two distinct phenotypes of the same disease

Clinically, a single stage-based protocol allows optimizing decisions in all cases