UPDATE ON DIAGNOSIS AND MANAGEMENT OF FETAL GROWTH RESTRICTION

Part I: Detection and consequences

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Dichorionic twins. Doppler UA N. Born 34 w
“Normal” development so far

1950 g (p45) 1200 g (p1)

Lagercrantz H. Better born too soon than too small. Lancet 1997
Placental insufficiency = high risk of IUFD and fetal/neonatal acidosis
Fetal Smallness = higher risk of placental insufficiency
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
5-15% during 3rd trimester
30% perinatal complications; 10-15% term stillbirth

- Stillbirth reduction OR 0.36
- Increase IUGR detection (IUGR > 36 w not diagnosed before)
1. Identify small fetus

2. Identify placental insufficiency (FGR vs. SGA)

3. Determine timing of delivery
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
  **FGR**
  Placental insufficiency

- Perinatal outcome normal - No IUFD NO signs of adaptation
  **SGA**
  Unknown (constitutional + others)

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

- Constitutionally small
- Placental insufficiency
- Extrinsic cause

SGA
FGR

1980-2000+: FGR = abnormal UA Doppler
(or why late onset small fetuses are mostly SGA)

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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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Early-onset IUGR

PROBLEM #2: (NEUROLOGICAL) MORBIDITY

Brain US anomalies in 30w IUGR

- Controls
- IUGR ant AoI
- IUGR REV AoI

- <29
- 29-32
- >32.0

- >90%
- 30-40%
- <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
Evidence #1: SGA HAVE POORER PERINATAL OUTCOMES

Perinatal adverse outcomes in SGA fetuses (n= 376)

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

Figuerras 2011
Evidence #2: “SGA” HAVE HIGHER RISK OF IUFD AT TERM

Stillbirth by relevant condition at birth (ReCoDe)
Gardosi et al. BMJ 2005 and 2013

**IUGR as relevant condition identified in 43-60%**
*Overall stillbirth rate (/ 1000 births) 4.2
2.4 in non-SGA VS. 19.8 in not detected*
Evidence #3: “SGA” HAVE POORER NEURODEVELOPMENT
Evidence #4: “SGA” HAVE CARDIAC REMODELLING

Cardiovascular programming in SGA / late-IUGR

Fetuses EFW<p10 at 5 years

Crispi 2010

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FGR = abnormal UA Doppler?

UA Doppler + (EARLY-ONSET)

UA Doppler N (LATE-ONSET)

Not anymore

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

Figueras 2012

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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%
FGR = EFW <p10 + any of

CPR <p5

UtA >p95

EFW CENTILE <3
Distribution of cases when FGR = abnormal UA Doppler

Savchev 2013

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Distribution of cases when FGR = abnormal CPR or UtA or EFW <p3
ISOLATED FETAL SMALLNESS = POORER PROGNOSIS
Perinatal and Long-term Outcomes

<table>
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<th>Poor perinatal outcome + IUFD (Doppler) Signs of adaptation</th>
<th>Perinatal outcome normal - No IUFD NO signs of adaptation</th>
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<td><strong>FGR</strong> Placental insufficiency</td>
<td><strong>SGA</strong> Unknown (constitutional + others)</td>
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FGR vs. SGA: DIFFERENT MANAGEMENT
1. Identify small fetus

2. Identify placental insufficiency (FGR vs. SGA)

3. Determine timing of delivery
Early-severe
High risk IUFD preterm

PROBLEM: TIMING DELIVERY
Q: Delivery? Next exam?

Late-mild
No IUFD <37w (risk at term)

PROBLEM: DETECTION
Q: Is it FGR or SGA?

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

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FGR = abnormal CPR or UtA or EFW <p3

Savchev 2013

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First goal: Identifying small fetus (EFW<p10)

Critical to detect FGR (=placental insufficiency)
Most cases occur at term

Second goal: Classify as FGR vs SGA

UA Doppler cannot be used as standalone criterion for FGR
FGR = SGA (<p10) + [ CPR or UtA or EFW<3 ]

Third goal: Decide timing of delivery.
UPDATE ON DIAGNOSIS AND MANAGEMENT OF FETAL GROWTH RESTRICTION
Part II: Integrated Management

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Small?

FGR?

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

Follow-up and delivery

- 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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FGR = abnormal CPR or UtA or EFW < p3

Management = when should we deliver?

Early-severe
High risk IUFD preterm

PROBLEM: TIMING DELIVERY
Q: Delivery? Next exam?

Late-mild
No IUFD < 37w (risk at term)

PROBLEM: DETECTION
Q: Is it FGR or SGA?
RATIONALE FOR AN INTEGRATED STAGE-BASED APPROACH TO THE MANAGEMENT OF FGR

PLACENTAL DISEASE

Diagnostic/chronic markers
DIFFERENCE FGR VS SGA

HYPOXIA

ACIDOSIS

SERIOUS INJURY

DEATH

Diagnostic/chronic markers
DIFFERENCE FGR VS SGA

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

Centralization

Diastolic failure

Systolic cardiac failure

BPP < 4

cCTG: reduced STV

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FGR = abnormal CPR or UtA or EFW<p3
umbilical artery
normal and abnormal hemodynamics

Cardiac pump
normal function

Cardiac pump
abnormal function

Placental status
<30%

placenta + cardiac ischemia
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.

\[
\text{IPUA} = p^{80} \quad \text{IPMCA} = p^{20} \quad \text{CPR} = p^{<5}
\]
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
RATIONALE FOR AN INTEGRATED STAGE-BASED APPROACH TO THE MANAGEMENT OF FGR

**PLACENTAL DISEASE**
- Diagnostic/chronic markers
  - DIFFERENCE
  - FGR VS SGA

**HYPOXIA**
- Centralization
- cCTG: reduced STV

**ACIDOSIS**
- Diastolic failure
- BPP < 4

**SERIOUS INJURY**
- Death

**DEATH**

**Stage fetal deterioration**
- I
- II
- III
- IV

**Risks of prematurity**
- Minimal
- MILD
- HIGH

**Indication about the short-term risk of IUFD/Brain injury**

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

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

- CPR <p5
- Ut A >p95
- EFW <p3

II. Severe placental resistance / redistribution

- AEDV
- Aol >p95

III. Severe hemodynamic adaptation
- Low suspicion acidosis

- DV >p95
- REDV

IV. High suspicion of acidosis
- High risk of death

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

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# FGR

## 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>&gt;90%</td>
<td>&lt;10%</td>
<td>50%</td>
<td>LOW</td>
</tr>
</tbody>
</table>

- **Risk of IUFD/brain injury**
  - LOW

- **Deliver at**
  - 37

- **Follow-up**
  - 1/w

- **Mode**
  - LI

- **EFW<p3, CPR <5, UtA>95**

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Stage 1
Recommended management: Delivery

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First goal:
Identify small fetus (EFW < p10)

Second goal:
Classify as FGR vs SGA using CPR, UtA and EFW < 3.

Third goal:
Decide timing of delivery and follow-up scheme: use a stage-based integrated protocol.
Early vs. Late onset FGR
FGR = low CPR or high UtA or EFW<p3 or low PI GF

EARLY FGR (1-2%)

PROBLEM: MANAGEMENT

Placental disease: high (UA+, PE high)
Hypoxia ++: systemic CV adaptation
Tolerance to hypoxia. Natural history
High mortality and morbidity

PROBLEM: DIAGNOSIS

Placental disease: low (UA-, PE low)
Hypoxia +/-: central CV adaptation
Low tolerance: no natural history
Low mortality but poor long outcome.

LATE FGR (5-6%)

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FETAL DETERIORATION IN PLACENTAL INSUFFICIENCY

PLACENTAL DISEASE

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

COMPENSATED HYPOXIA

DECOMPENSATED HYPOXIA

- Cardiac ischemia
- Diastolic failure
- DUCTUS VENOSUS >p95 and a-
- cCTG: reduced short-term variability
- CTG ABNORMAL
- Systolic cardiac failure

SERIOUS INJURY DEATH

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

PLACENTAL DISEASE

Increment placental impedance

UTERINE A. >p95

CPR <p5

UMBILICAL A. >p95

CENTRALIZATION

MIDDLE CEREBRAL A. <p5

Ao ISTHMUS >p95

growth

mild hypoxia
no cardiovascular adaptation

COMPENSATED HYPOXIA

minimal tolerance to hypoxia

Placental injury <30%

DECOMPENSATED HYPOXIA

cardiac ischemia
Diastolic failure

DUCTUS VENOSUS >p95 and a-

SERIOUS INJURY
DEATH

CTG / BPP ABNORMAL

Systolic cardiac failure

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When and how to deliver
FGR = 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)

Stage II to IV
PROTOCOL

Stage I
>37w

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Early-onset FGR
PROBLEM #1: MORTALITY

- 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
  Baschat 2007, Kafur 2008, Lalor 2010,

Perinatal Mortality
- <26: >90%
- 26-28: 30-40%
- 29-30: <10%
- 31-34: Stage II

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Early-onset FGR

PROBLEM #2: (NEUROLOGICAL) MORBIDITY

Neonatal brain US anomalies in 30-34w FGR

- Controls
- IUGR ant AoI
- IUGR REV AoI

Neurological Morbidity

- <29
- 29-32
- >32.0

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

Fouron 2004
Del Rio 2008
Cruz-Martinez 2012

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Late-onset FGR
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)