Severe early onset intra-uterine growth restriction

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University College London
Outline

• What is severe early onset IUGR?
• How do we manage IUGR?
• How can we counsel women?
• What can we do about it?
IUGR is not the same as SGA

• 8% pregnancies

• Contributes to 50% of stillbirths

• Most due to uteroplacental insufficiency
Uteroplacental insufficiency

- Trophoblast invades the spiral arteries

- In IUGR there is less trophoblast invasion

Moffett-King A, 2002
Uteroplacental insufficiency

Human pregnancy

Uterine blood flow (ml/min)

Gestational Age (Weeks)

Konje et al. 2003
Severe early onset IUGR

- 1:500 pregnancies
- Delivery or stillbirth by 28 wks
- Currently no treatment
Between 23 and 26 weeks of gestation, an increase in birthweight of 100g reduces the risk of dying by 40%.

Baschat et al 2007
The cost of severe IUGR

- The cost of caring for babies to discharge
  - £39,483 / €45,397, this is 50% higher than babies born weighing over 1000g
- Increasing the gestational age at birth by 1 week will reduce costs by 30% over the early preterm range

<table>
<thead>
<tr>
<th>Long Term Costs</th>
<th>Cost of child surviving to age 18 years £</th>
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<tbody>
<tr>
<td>Term survivor</td>
<td>1</td>
</tr>
<tr>
<td>Preterm survivor &lt;37 weeks</td>
<td>23,284</td>
</tr>
<tr>
<td>Very preterm survivor &lt;33 weeks</td>
<td>62,859</td>
</tr>
<tr>
<td>Extremely preterm survivor &lt;28 weeks</td>
<td>96,393</td>
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</table>
How do we manage IUGR?
Patient pathway

Prediction: history, biomarkers, uterine artery Dopplers → Identification of SGA

Assess risk factors at booking
If major risk factors OR >2.0 then USS from 26-28/40
If 3 or more minor risk factors then Ut Art Doppler at 20-24/40

Potential Interventions
- Heparin
- Smoking cessation
- Start antiplatelets <16/40 if risk factors for PET
  - May have benefit for preventing SGA
    - but not enough evidence yet
  - Systematic reviews suggest RR for SGA neonate is 0.90 (0.83-0.98)

Use AC or EFW
- Customised charts of EFW may improve detection and outcomes

OR >2.0
- Maternal age >40 yrs
- Smoker or cocaine use
- Previous SB or SGA
- Maternal or paternal SGA
- HT, APS, DM, renal failure
- Heavy APH
- Echogenic bowel
- PET or severe PIH
- Low PAPP-A (<0.4 MoM)
- Low maternal weight gain
- Daily vigorous exercise
**Patient pathway**

- **Prediction:** history, biomarkers, uterine artery Dopplers
- **Identification of SGA**
  - Detailed assessment of anatomy
  - Uterine artery Dopplers
  - Karyotype (amnio, free fetal DNA, microarrays)
  - Screen for congenital infections
  - Diagnosis of IUGR due to uteroplacental insufficiency

- **If severe <23/40 offer karyotype**
- **If severe screen for congenital infection**
  - CMV and toxoplasmosis
  - Consider syphilis and malaria
- **If 18-20/40 refer to FMU for detailed anatomy and Uterine Artery Dopplers**
Patient pathway

Prediction: history, biomarkers, uterine artery Dopplers

Identification of SGA

- Detailed assessment of anatomy
- Uterine artery Dopplers
- Continuous assessment prognosis
- Maternal complications (PET, HELLP)

Diagnosis of IUGR due to uteroplacental insufficiency

- Karyotype (amnio, free fetal DNA, microarrays)
- Screen for congenital infections

Ultrasound monitoring of fetal growth and wellbeing

- Gestation
- Neonatal input

Decision to terminate

Stillbirth

Decision to deliver

Parental opinion
Ultrasound assessment in severe IUGR

- Raised Umbilical artery PI
- Absent or reversed EDF
- Raised Uterine artery PI

Degree of uteroplacental insufficiency
Umbilical artery Dopplers

Soothill 1993
• Raised umbilical artery PI predicts hypoxic morbidity in SGA <2.5th centile

Meta-analysis Morris 2011
• Predicts SGA, wellbeing and outcome in high risk

SGA < 2SD of mean (n=7)
Perinatal mortality (n=21)
Neonatal morbidity (n=7)
Acidosis (n=12)

<table>
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<tr>
<th>Condition</th>
<th>Positive Likelihood Ratio</th>
</tr>
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<tbody>
<tr>
<td>Acidosis (n=12)</td>
<td>2.75</td>
</tr>
<tr>
<td>Neonatal morbidity (n=7)</td>
<td>3.05</td>
</tr>
<tr>
<td>Perinatal mortality (n=21)</td>
<td>2.50</td>
</tr>
<tr>
<td>SGA &lt; 2SD of mean (n=7)</td>
<td>4.37</td>
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</tbody>
</table>

Graph:
- Umbilical Artery PI
- FHR
- Biophysical Profile
- AGA
- SGA

Positive Likelihood Ratio

0.01 0.1 1 10 100
Ultrasound assessment in severe IUGR

- Raised Umbilical artery PI
- Absent or reversed EDF
- Raised Uterine artery PI
- Raised ductus venosus PI
- Absent or reversed a wave
- Umbilical vein pulsation
- Reduced middle cerebral artery PI
- Reduced cerebro-placental ratio

Degree of uteroplacental insufficiency

Fetal response
Cerebral vasodilatation or “brain-sparing” is a compensatory mechanism in response to chronic hypoxia.

The adaptation of brain sparing is complex and is associated with poorer neurodevelopmental outcome, even in “mild” IUGR.

Benavides-Serralde et al 2011, Figueras et al 2011
Cerebro-placental ratio: UA PI/MCA PI

Relationship between abnormal CPR <5\textsuperscript{th} centile, days from last Doppler evaluation to delivery, and adverse perinatal outcomes in IUGR fetuses

Kaplan-Meier survival estimates by cerebro-placental ratio

Proportion with adverse outcome

CPR >5\textsuperscript{th} centile

CPR <5\textsuperscript{th} centile

Days from last Doppler to delivery

Odibo et al 2005
Ductus venosus
Ductus venosus

Turan et al, 2007
DV PI predicts fetal acidosis at birth in IUGR fetuses

Turan et al, 2011
Duration of absent/reversed a-wave predicts stillbirth
Ductus venosus

Baschat 2007

• Gestational age
  – Survival <26+6
  – Intact survival <29+2

• Absent/reversed DV a-wave
  – Intact survival >29+2 & 600g

\[\text{Positive a-wave}
\]
\[\text{Absent or reversed a-wave}\]
Sequence of Doppler changes

Turan 2008

- Characterised three patterns of Doppler changes

<table>
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<tr>
<th>Placental insufficiency</th>
<th>Sequence of Doppler abnormalities</th>
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</table>
| Mild  
  \(n = 34\)        | \(\uparrow\) UA 33 days \(\downarrow\) CPR |
| Progressive  
  \(n = 49\)  | \(\uparrow\) UA 19 days \(\downarrow\) CPR 14 days Brain sparing 4 days UA A/REDV 14 days \(\uparrow\) DV 8 days DV-RAV/UV pulsation |
| Severe early-onset  
  \(n = 21\)   | \(\uparrow\) UA 7 days \(\downarrow\) CPR 9 days UA A/REDV 7 days Brain sparing 11 days \(\uparrow\) DV 5 days DV-RAV/UV pulsation |
Ultrasound assessment in severe IUGR

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Degree of uteroplacental insufficiency

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Ultrasound assessment in severe IUGR

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- Fetal response

Degree of uteroplacental insufficiency

Fetal response
Ultrasound assessment in severe IUGR

- Raised Uterine artery PI
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Degree of uteroplacental insufficiency

Gestation + EFW

Timing of steroids and delivery

Fetal response

Timing of steroids and delivery
RCOG Guidelines: Preterm SGA

• Scan for growth velocity at least 3 weeks apart
• Umbilical artery Doppler = 1° surveillance
  – Twice weekly if PI > 2SD
  – Daily if Absent or Reversed EDF
• If abnormal, monitor DV to time delivery

• Don’t use:
  – CTG, amniotic fluid or BPP as sole surveillance
  – MCA to time delivery
Timing of delivery

- **<26+6**
  - Gestation best predictor of survival

- **<29+2**
  - Gestation best predictor of intact survival
  - If abnormal DV or UV pulsations deliver after steroids if viable birthweight

- **30-32**
  - Consider delivery if umbilical artery AREDF

- **>32**
  - If SGA with abnormal umbilical artery Doppler diagnosed
    - >32/40 deliver by 37/40
Timing of delivery

**GRIT**
Stillbirth in delayed delivery balanced by neonatal death in immediate delivery
Higher CP in immediate <30/40 at 2 yrs, no difference in neurodevelopment at 6-9 yrs

- **<26+6**
  Gestation best predictor of intact survival
  - If abnormal DVPI or absent/reversed a wave?

- **<29+2**
  Gestation best predictor of intact survival
  - If abnormal DV or UV pulsations deliver after steroids if viable

- **30-32**
  Consider delivery if umbilical AREDF

- **>32**
  If SGA with abnormal umbilical artery Doppler diagnosed
  >32/40 deliver by 37/40

**TRUFFLE**
abnormal DVPI or absent/reversed a wave?

**Aortic Isthmus**
Does it have a role in predicting intact survival?
How can we counsel women?
UCLH 12 year retrospective audit

- 694 cases <5\textsuperscript{th} centile 18+0-23+6
What can we tell women with mid-trimester SGA?

- 39%: Constitutionally small or not small
- 38%: Obvious abnormality
- 13%: Probable abnormality
- 10%: Further tests show abnormality
Early uteroplacental IUGR

First gestation at which biometry <5th and UAPI >95th
Perinatal variables and neonatal outcomes in severely growth restricted preterm fetuses

NEELAM ENGINEER\textsuperscript{1} & SAILESH KUMAR\textsuperscript{1,2}

- 60 pregnancies
- 7 MTOP
- 9 IUD
- 44 livebirths
- <3\textsuperscript{rd} centile
- Abnormal arterial or venous Dopplers
- Diagnosed 18 - 34+2
- Born 25 - 35+6
- 31 developed PET
- 6 NND
- 38 survived (63%)
Early onset, severe fetal growth restriction with absent or reversed end-diastolic flow velocity waveform in the umbilical artery: Perinatal and long-term outcomes

Scott G. PETERSEN, Shell F. WONG, Prashanth URS, Peter H. GRAY and Glenn J. GARDENER

36 pregnancies

- 19 IUD (53%)
- 17 liveborn

12 died in delivery room or NICU
- 5 survived to discharge (14%)

9 Severe PET / HELLP
- 4 admitted to ICU
- 10 classical sections

- <10th centile
- <500g
- UA AREDF
- Median gestation 24 (18 - 29)
What can we tell women with mid-trimester uteroplacental IUGR?

• Serial scans help define progression and severity

• Very little evidence on outcome
  – Perinatal mortality about 50%
  – Maternal morbidity

  – What about neonatal mortality, morbidity and neurodevelopment?
What can we do about it?
Treatment that doesn’t work

- Bedrest
- Maternal oxygen supplementation
- Maternal nutritional supplements
- Low-dose aspirin
- β-blockers
- Calcium channel blockers
- Plasma volume expansion
- Nitric oxide donors e.g. GTN
- L-arginine
- Vitamin C
Future treatment?

• Sildenafil citrate (STRIDER)
  – Uterine artery vasodilatation
  – Increased AC velocity (n=9)

• Melatonin
  – Antioxidant and vasoactive
  – Neuroprotection in IUGR
  – Effects on fetal growth in rats and sheep
Does vascular endothelial growth factor gene therapy safely improve outcome in severe early-onset fetal growth restriction?

http://www.euram.ltd.uk/EVERREST/index.html
Delivery of adenovirus containing VEGF gene to uteroplacental circulation

- **Local** over-expression of VEGF
  - Alter uterine artery vascular tone & angiogenesis
    - Increase uterine blood flow
      - Increase fetal growth in severe IUGR
Summary

• SGA is not IUGR
• Severe early onset IUGR has high mortality and morbidity
• Timing of delivery is challenging at early gestations
• Abnormal DV reflects fetal decompensation but neurodevelopment may already have been impaired
• An effective treatment is needed