Interventions aiming to treat fetal growth restriction
and the EVERREST EU-project

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Fetal Growth Restriction

- Complicates ~8% of pregnancies (severe 1:500)
- Major cause of perinatal mortality & morbidity
- No effective treatment
- Outcome dependent on gestational age
- Early-onset severe IUGR associated with reduced uterine blood flow
Uteroplacental perfusion

Uteroplacental blood flow is proportional to fetal size

Uteroplacental insufficiency

(Konje et al. 2003)
Between 23 and 26 weeks of gestation, an increase in birthweight of 100g reduces the risk of dying by 40%.
Very preterm IUGR – high survival:
- Lund / Malmö 90%
- TRUFFLE study 94%

**HOWEVER**

- both the short-term and long-term morbidity is considerably high!

- cognitive impairment
- behavioural disturbances
- reduced lung function
- changes in cardiovascular function
Early-onset IUGR

Postnatal growth stimulation of IUGR infants difficult.

It is desirable to improve fetal growth and to prolong pregnancy.

Need for intrauterine therapy.
Therapies that do not work

- Bedrest
- Maternal oxygen supplementation
- Maternal nutritional supplements
- Low-dose aspirin
- $\beta$-mimetics (RCTs show no effect)
- Calcium channel blockers
- Plasma volume expansion
- Vitamin C
Interventions aimed at increasing uterine blood flow

*L-arginine* (aminoacid, nitric oxide donor)

- Maternal intravenous infusions
- L-arginine readily available and safe in pregnant women, however, conflicting data on increase in birth weight
- Currently not recommended for treatment of IUGR
Interventions aimed at increasing uterine blood flow

**Sildenafil citrate** (nitric oxide donor)

- Temporary smooth muscle relaxation in vessels
- Works in animal models and tested in humans
- In severe, early-onset IUGR thrice daily maternal treatment with 25 mg sildenafil until delivery = ↑ AC growth velocity
- Randomized controlled trial data required
Growth hormone treatment

- Animal models
- Maternal and fetal supplementation
- Risk of adverse effects (hydranencephaly in fetuses)
Insulin-Like Growth Factor-1 (IGF-1)

• Implicated in regulation of normal placental function and of appropriate fetal and postnatal growth

• Anabolic effect, stimulates substrate uptake and inhibits protein breakdown
IGF-1 treatment

Maternal

Guinea pigs

• Increased placental mass and functional capacity of placenta = ↑ fetal growth
• Significant effects on maternal physiology
IGF-1 treatment

Fetal infusion

Sheep and non-human primates

• Increased aminoacid utilization and alteration in fetal protein accretion

• Adequate substrate supply necessary for effective tissue growth

• Organ specific increases in growth, however no significant effect on body size and growth
IGF-1 treatment

*Intra-amniotic*

**Sheep**

- Increased total fetal growth rate and organ growth in growth restricted fetal sheep
- Up-regulates placental amino acid transporters
- Promising approach (?)
Vascular Endothelial Growth Factor (VEGF)

Maternal uterine artery VEGF gene therapy

...and the EVERREST study
VEGF implicated in trophoblast invasion

Over-expression of sFlt1 in pregnant mice using adenovirus causes PE-like syndrome & IUGR

Pre-eclampsia

IUGR

sFlt-1 ↑

VEGF ↓

PIGF ↓

Reduced endothelial derived vasodilatation

endothelial dysfunction
Gene therapy……

....uses genetic material as a drug delivery vehicle to facilitate the expression of therapeutic proteins

✓ Achieve targeted protein expression
  • Uteroplacental circulation
✓ Short term protein expression
  • Adenovirus vectors
VEGF levels are reduced in fetal growth restriction

Sustained local levels of VEGF will treat fetal growth restriction

“Maternal growth factor gene therapy”
Hypothesis
Delivery of adenovirus containing VEGF gene to uteroplacental circulation

Local over-expression of VEGF

Increase uterine blood flow

Alter uterine artery vascular tone & angiogenesis

Increase fetal growth in severe FGR
Short-term changes in uterine artery volume flow 4 – 7 days after vector injection

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Before injection</th>
<th>After injection</th>
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<tbody>
<tr>
<td>VEGF-A</td>
<td>408 ± 273</td>
<td>1321 ± 727</td>
<td></td>
</tr>
<tr>
<td>lacZ</td>
<td>561 ± 281</td>
<td>755 ± 193</td>
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Two way analysis of variance

*p < 0.005

David et al, 2008, Human Gene Therapy
Long-term changes in uterine artery blood flow after vector injection

VEGF-A vessels vs LacZ at 30 days after injection

p=0.012 Two-way ANOVA
Correcting growth restriction in animal models of IUGR

*IUGR sheep*: adolescent overfed ewe, Rowett Institute, Aberdeen
- efficacy, fetal growth, neonatal outcome and safety

*IUGR guinea pig*: maternal nutrient restriction model
- fetal growth, vector dose and safety
Fetal Growth Velocity - abdominal circumference

Mean surgery day

*** p=<0.001

Control (n=12) | VEGF (n=18) | Saline (n=13) | LacZ (n=14)

Gestation (days)

Abdominal circumference (mm)
Proportion of very small sheep fetuses >2SD below control mean

(Control mean = 5084g, SD = 431g, -2SD cut-off = 4222g)

p = 0.033
(Fisher’s exact test)
Safety

No significant changes in:
Maternal heart rate, blood pressure
Fetal heart rate, blood pressure
No vector spread
No fetal abnormalities

Abi-Nader et al, Lab Animals, 2011
EVERREST

• Does vascular endothelial growth factor gene therapy safely improve outcome in severe early-onset fetal growth restriction?

Our aim

• To translate a novel gene medicine delivered to mothers, into the clinic, so as to improve fetal growth in severe early-onset fetal growth restriction
EVERREST

- Reproductive toxicology
- Bioethics study
- First-in-woman phase I/IIa safety/efficacy study
Human placenta toxicology studies

After regeneration of syncytiotrophoblast, placental villous explants are exposed to high dose adenovirus vector

Perfusion experiments in normal and IUGR human placentae with high dose adenovirus vector
First-in-woman trial
First-in-woman trial

- 4 EU recruiting centres
  (London, Hamburg, Lund, Barcelona)

- Inclusion criteria:
  - Severe early-onset IUGR
  - ≥22 weeks of gestation
  - Uteroplacental insufficiency (abnormal blood flow)
  - Other causes of IUGR excluded

- Vector delivered via interventional radiology
Treatment

- Vector instilled into uterine artery for 2 minutes using interventional radiology approach
EVERREST outcome measures

Primary outcome

• Assessment of patient safety and tolerability

Secondary outcomes

• Uterine artery volume blood flow
• Abdominal and head circumference (ultrasound)
• Gestational age at delivery
• Birth centile
• Maternal blood pressure and proteinuria
• Composite clinical outcomes
• Myometrial artery contractility and placental phenotype
Summary

- Local expression of VEGF in the uterine arteries
  - increases uterine blood flow
  - alters vascular reactivity
  - increases angiogenesis
  - improves fetal growth in IUGR pregnancies
  - without apparent maternal or fetal harm

- VEGF gene therapy promising as a therapy for severe early-onset IUGR
Thank you!
University College London, UK
A David et al, Gene Therapy 2008
V Mehta et al, Gene Therapy 2011

original idea

- Increase uterine artery blood flow short and long term
- Relax uterine arteries
- Increase endothelial nitric oxide synthase
- Increase endothelial cell proliferation in uterine artery adventitia
- No vector spread to fetus
- No acute haemodynamic changes
University College London, UK

D Carr et al, Hum Gene Ther 2014

original idea

Increase fetal growth velocity
Mitigate “brain sparing”
No adverse events at delivery or up to 3 months postnatally
Planned clinical vector has similar effects