The STRIDER: Het kan ook anders lopen - lessons learned
Conflicts of interest

affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter:

NONE
How can we approach one topic in an international setting?

The STRIDERs as an example
Early FGR

*easy to diagnose, difficult to treat*

Antenatal clues
- A uterina
- A umbilicalis
- A cerebri media
- Ductus venosus
- Aorta, a Mesenterica
- Asymmetric FGR
- ‘Crossing the centiles’
- Maternal hypertensive disorders
- Fetal movements
- Serum biomarkers

Rare: Affects ± 0.4%
Mortality: HIGH!
Placental insufficiency

Incomplete spiral artery remodelling first trimester

→

Increased uteroplacental vascular resistance

Bell, Nature Reviews Immunology 2004
Altering uterine blood flow

Groom and David AJOG 2017
Altering uterine blood flow

Diagram showing the mechanisms involving Nitric Oxide, Guanylate Cyclase, cGMP, and Sildenafil, illustrating how they interact to alter blood flow.
Animal studies

Pregnancy and Hypertension

Sildenafil During Pregnancy
A Preclinical Meta-Analysis on Fetal Growth and Maternal Blood Pressure

Nina D. Paauw, Fieke Terstappen, Wessel Ganzvoort, Jaap A. Joles, Hendrik Gremmels, A. Titia Lely
Pre-RCT evidence

- Used in pregnancy for maternal pulmonary arterial hypertension with no identified safety concerns
- Commonly used as an adjunct to iNO therapy for persistent pulmonary hypertension of the newborn (PPHN), a recognised complication of preterm birth
- Animal data
- Early human data very promising
- ‘Back against the wall’
- ‘Creep into practice’
STRIDERs

Sildenafil Therapy In Dismal prognosis Early-onset intrauterine growth Restriction

2011 proposal for worldwide STRIDER pilot trial
Early move to individual country trials
- Individual trials, independently funded & executed, publication
- Variations in inclusion criteria and outcomes but clearly defined
- Shared resources and support
- Planned individual participant data (IPD) meta-analysis
- Outcomes include immediate short outcomes and long-term

Ganzevoort Systematic Reviews 2014
Pels BMC Preg Childbirth 2017
Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial

Andrew Sharp, Christine Cornforth, Richard Jackson, Jane Harrold, Mark A Turner, Louise C Kenny, Philip N Baker, Edward D Johnstone, Asma Khalil, Peter von Dadelszen, Aris T Papageorghiou, Zarko Alfrevic, on behalf of the STRIDER group

Summary

Background Severe early-onset fetal growth restriction can lead to a range of adverse outcomes including fetal or

Interpretation Sildenafil did not prolong pregnancy or improve pregnancy outcomes in severe early-onset fetal growth restriction and therefore it should not be prescribed for this indication outside of research studies with explicit participants’ consent.
A Randomised Controlled Trial of Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction (New Zealand and Australia)

Dr Katie Groom, Professor Lesley McCowan, Dr Arier Lee, Professor Peter Stone, Professor Philip Baker
<table>
<thead>
<tr>
<th>Strider NZAUS</th>
<th>Sildenafil (n=63)</th>
<th>Placebo (n=59)</th>
<th>Odds ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in fetal growth velocity pre- and post-treatment</td>
<td>32/61 (52.5)</td>
<td>39/57 (68.4)</td>
<td>0.49 (0.23-1.05)</td>
</tr>
</tbody>
</table>

**Abdominal circumference z-scores**

- p=0.61

No difference in fetal growth throughout treatment
STRIDERs

Recruitment complete July 2016
n=130/112

Recruitment complete March 2017
n=216/354
n=122/122

Ireland
closed
n= 21/90

Canada

UK

Netherlands

NZAus

Recruitment complete March 2017
n=216/354
And then....

The Guardian: II lasta kuoli, kun raskaana oleville naisille annettiin Viagraa lääketestissä Hollannissa

In a British study, this year a positive effect of using Viagra on the baby’s head growth rate. Did the Amsterdamse observers stop the experiment due to safety reasons?
During planned interim analysis the Data Safety Monitoring Board advised to discontinue trial:

“... serious concern that sildenafil may cause harm to the newborn children...”

“... given the results of 182 children it is extremely unlikely that any benefit can be shown on the primary endpoint if the trial is continued to its completion...”

- Excess of pulmonary hypertension of neonate
- Associated with deaths
- NO benefits observed
- Also not in other trials
What to conclude?

- No difference in primary outcome
- No difference in overall mortality
- More pulmonary hypertension in liveborn neonates in sildenafil group

Possible mechanism:
- rebound effect, structural changes, chance
The future of STRIDERs

How to move on?

• Translational studies

• IPD MA
  • Primary outcome:
    • Survival free of neurosensory impairment at 2-3 years of age
  • Subgroups
  • Power of numbers
De vraag van vandaag

Wat als het niet loopt zoals verwacht/gehoopt, hoe ziet het vervolg er uit?
Wat zijn de lessons-learned als je met je project wereldnieuws wordt? Hoe pak je dat aan?

• Patiënten
  • Pro-active communication
  • Show commitment, responsibility, transparency
• Instanties, IGJ, RvB, METC, voorlichting, ZonMW
• Collega’s
• Journalisten

• Bemensing, financiering
Toekomst

- Samenwerking (dankzij...)
- Bemensing
- Financiering
  - Voldoen aan alle regelgeving
  - Nieuwe realiteit AVG etc.
  - Time-to-start
- Maar....
  - Het moet wel gebeuren or else....