COGEN Symposium III
Barcelona

Presentation by
Alastair Sutcliffe – Children’s Doctor

Wednesday, 27 September 2017
Children conceived with ART:

“Its hardly a Darwinian way of reproducing”

Dave, taxi cab driver
Nottingham, England
Children as research subjects: congenital anomalies?
Children born after preimplantation genetic screening and diagnosis
<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>PGD/PGS</th>
<th>Sample</th>
<th>Age/Follow-up</th>
<th>Results</th>
</tr>
</thead>
</table>
| Banerjee et al. 2008| Neurodevelopmental scoring  
Family functioning  
Initial evidence of growth problems or other physical abnormalities | PGD     | United Kingdom  
PGD: n=49  
NC: n=66 | 3 to 56 months old | NS  
*Except PGD children were more likely to LBW and premature. |
<table>
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</table>
| Nekkebroek et al. 2008 | Mental, motor, language and socio-emotional | PGD/PGS combined in one group | singletons  
PGD/PGS: n=41  
ICSI: n=35  
NC: n=53 | 2 years old | NS                               |
| Desmyterre et al. 2009 | Mental, motor, language and socio-emotional | PGD/PGS combined in one group | twins  
PGD/PGS: n=16  
ICSI: n=16  
NC: n=15 | 2 years old | NC lower than PGD/PGS for language development |
| Nekkebroek et al. 2011 | Mental, motor, language and socio-emotional | PGD/PGS combined in one group | PGD: n=47  
ICSI: n=50  
NC: n=55 | 5-6 years old | NS                               |
| Seggers et al. 2013 | Cardiometabolic outcomes | IVF/ICSI with or without PGS | PGS: n=49  
IVF/ICSI no PGS: n=64 | 4 years old | NS  
*PGS received more paramedical care |
| Winter et al. 2015 | Psychosocial functioning | PGD | Singletons  
PGD: n=47  
ICSI: n=50  
NC: n=55 | 5-6 years old | NS                               |
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<tr>
<td>Middelburg et al. 2011</td>
<td>Mental, psychomotor neurologic and behavioural</td>
<td>IVF/ICSI + PGS/no PGS</td>
<td>Netherlands—singletons and twins PGS: n=54 No PGS: n=77</td>
<td>2 years old</td>
<td>NS * PGS: lower neurological optimality scores (NOS)</td>
</tr>
<tr>
<td>Schendelaar et al. 2013</td>
<td>Neurologic, cognitive and behavioural</td>
<td>IVF/ICSI + PGS/no PGS</td>
<td>Netherlands—singletons and twins PGS: n=49 (9 pair twin) No PGS: n=64 (11 pair twin)</td>
<td>Follow-up of previous study at 4 years old.</td>
<td>NS *For twins: lower fluency scores and NOS</td>
</tr>
<tr>
<td>Thomaidis et al. 2012</td>
<td>Physical, developmental and neurological</td>
<td>PGD</td>
<td>Greece N=31</td>
<td>2 months to 7.5 years old</td>
<td>Frequency rates suggest poorer cognitive and motor skills in PGD</td>
</tr>
<tr>
<td>Sacks et al. 2016</td>
<td>Neuropsychological assessment</td>
<td>PGD</td>
<td>Pilot study N=27 triplets and twins</td>
<td>4 to 5 years old</td>
<td>NS</td>
</tr>
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</tr>
<tr>
<td>Hasson et al. 2017</td>
<td>Obstetric and neonatal outcomes including malformation</td>
<td>IVF/ICSI + PGD/no PGD</td>
<td>Israel PGD: n=89 No PGD: n=166</td>
<td>Children born 2002-2010 Birth and neonatal outcomes</td>
<td>NS</td>
</tr>
<tr>
<td>Bay et al., 2016 *Registry Based Study</td>
<td>Obstetric and neonatal outcomes including malformation</td>
<td>PGD</td>
<td>Danish registry PGD: n=149 IVF/ICSI: n=36,115 NC: n=909,624</td>
<td>Children born 1999-2013 Birth and neonatal outcomes</td>
<td>NS *differences only found in PGD due to parental monogenetic disorders (n=58). Increased obstetric complications + longer neonatal admissions</td>
</tr>
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<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Eldar-Geva et al 2014</td>
<td>Obstetric and neonatal outcomes including malformation</td>
<td>PGD vs controls</td>
<td>Israel</td>
<td>Children born 2005-2012</td>
<td>Birth and neonatal outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PGD: n=242 ICSI: n=242 NC=733</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Summing up...**

* Small and/or convenience samples
* Limited inclusion of confounders
* A single follow-up at age 4-5 and 7.5

**Implications...**

- Cost-effectiveness
- Adapted informed consent
- Large population-based studies
- Longitudinal studies with longer follow-ups
- Including underlying parental conditions
Questions asked by parents

- Infertility: 24
- General health: 8
- Telling child: 5
- Frozen embryo: 4
- Dyslexia: 3
- Hyperactivity: 2
- UTI: 2
- Short stature: 2
- Food allergy: 2
- Dyspraxia: 2
- Hearing: 2
- Development: 2
- Education potential: 2
- Social skills: 2
- Personality: 2
- Weight gain: 2
- Painful genitalia: 2
- Asthma: 2
- Leukaemia: 2
- Rheumatic disorders: 2
- Press issues: 2
Childhood Cancer
Childhood Cancer
Cancer risk in children born after assisted conception

Dr Carrie Williams, Mrs Kathryn Bunch, Mr Charles Stiller, Dr Mike Murphy, Dr Bev Botting, Prof Hamish Wallace, Dr Melanie Davies & Dr Alastair Sutcliffe
Why Investigate this potential risk?

- Parental Concern
- Potential altered epigenetic patterns
  - ART embryos/ Cord blood/ placenta
- Children with Imprinting Disorders
- Epigenetics & carcinogenesis
  - As part of Imprinting disorders
  - Independently of Imprinting disorders
Large population based linkage study

- Records all UK ART cycles and outcomes
- Reporting is a legal requirement

- Largest population based registry worldwide
- Complete population coverage
<table>
<thead>
<tr>
<th>HFEA</th>
<th>NRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>106,381 children</td>
<td>14,896 children</td>
</tr>
<tr>
<td>Born in England, Wales or Scotland</td>
<td>Born in England, Wales or Scotland</td>
</tr>
<tr>
<td>After non-donor ART</td>
<td>Developed cancer before 15\textsuperscript{th} birthday or before 1/1/2009</td>
</tr>
<tr>
<td>Broad Deterministic Linkage</td>
<td>Probabilistic Linkage</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Using DOB, Birth weight, Parental DOB</td>
<td>Using Parental Names</td>
</tr>
<tr>
<td>Over 4 million potential matches</td>
<td>3,949 above pre-set accuracy threshold</td>
</tr>
</tbody>
</table>
Analysis

- Person years at risk determined
  - 106,013 children, 700,705 years

- Expected cases calculated
  - Based on annual age-specific incidence 1992-2008

- Observed vs. expected = SIR

- Stratified by potential mediating/moderating factors

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancers</td>
<td>108</td>
<td>109.7</td>
<td>0.98</td>
<td>0.81-1.19</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>34</td>
<td>37.5</td>
<td>0.91</td>
<td>0.63-1.27</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>22</td>
<td>25.8</td>
<td>0.85</td>
<td>0.54-1.29</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>9</td>
<td>10.2</td>
<td>0.88</td>
<td>0.40-1.68</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>&lt;5</td>
<td>5.1</td>
<td>0.59</td>
<td>0.12-1.73</td>
</tr>
<tr>
<td>Renal tumors</td>
<td>8</td>
<td>8.5</td>
<td>0.94</td>
<td>0.41-1.86</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>6</td>
<td>1.9</td>
<td>3.27</td>
<td>1.20-7.12</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>&lt;5</td>
<td>1</td>
<td>2.95</td>
<td>0.61-8.62</td>
</tr>
<tr>
<td>Ewing's</td>
<td>&lt;5</td>
<td>1.6</td>
<td>2.47</td>
<td>0.67-6.32</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>10</td>
<td>3.8</td>
<td>2.62</td>
<td>1.26-4.82</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>&lt;5</td>
<td>3.6</td>
<td>0.56</td>
<td>0.07-2.03</td>
</tr>
</tbody>
</table>
No difference when stratified by:
- Sex
- Age
- Birth weight
- Gestation
- Multiple births
- Parity
- Parental ages
- Type of ART
- Fresh vs. cryopreserved cycle
- Cause of parental infertility
<table>
<thead>
<tr>
<th>Mediating/ Moderating Factor</th>
<th>Person Years</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>701,165</td>
<td>3.64</td>
<td>1.34-7.93</td>
</tr>
<tr>
<td>Birth Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500g</td>
<td>218,240</td>
<td>10.29</td>
<td>3.34-24.02**</td>
</tr>
<tr>
<td>2500-3999g</td>
<td>440,482</td>
<td>0.95</td>
<td>0.02-5.28</td>
</tr>
<tr>
<td>≥4000g</td>
<td>36,645</td>
<td>0.00</td>
<td>0.00-32.03</td>
</tr>
<tr>
<td>ART type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVF</td>
<td>469,995</td>
<td>5.18</td>
<td>1.68-12.08*</td>
</tr>
<tr>
<td>ICSI (+ micromanipulation)</td>
<td>220,674</td>
<td>1.56</td>
<td>0.04-8.71</td>
</tr>
<tr>
<td>Not Recorded</td>
<td>10,496</td>
<td>0.00</td>
<td>0.00-85.57</td>
</tr>
<tr>
<td>Cycle type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh</td>
<td>623,876</td>
<td>3.44</td>
<td>1.12-8.02*</td>
</tr>
<tr>
<td>Cryopreserved</td>
<td>76,218</td>
<td>5.24</td>
<td>0.13-29.21</td>
</tr>
<tr>
<td>Not Recorded</td>
<td>1,071</td>
<td>0.00</td>
<td>0.00-1381</td>
</tr>
</tbody>
</table>
Rhabdomyosarcoma

- 10 Observed vs. 3.8 expected
- SIR = 2.62 (95% CI 1.26-4.82)

- No difference when stratified by:
  - Age
  - Birth weight
  - Gestation

- No clear explanation for significantly increased risk
  - Chance?
  - Imprinting Disorders?

SUMMARY

- No overall increased risk

- No difference when stratified for potential mediating/moderating factors
  - Small increased risk of Hepatoblastoma
    - Absolute excess risk = 5.94/ million person years at risk
    - Associated with low birth weight
  - Small increased risk of Rhabdomyosarcoma
    - Absolute excess risk = 8.82/ million person years at risk
    - Rhabdomyosarcoma associated with imprinting disorders but not found in this study

Dr Carrie Williams
Dr Beverley Botting (Statistical Supervisor)

Co-Authors
- Mrs Kathryn Bunch, Dr Charles Stiller, Dr Mike Murphy (NRCT, CCRG, Oxford University) Dr Melanie Davies (UCLH fertility units)
- Professor Hamish Wallace (Paediatric Oncology, Edinburgh University)

British Fertility Society Members
HFEA Staff

Great Ormond street and UCL INSTITUTE OF CHILD HEALTH

NHS
National Institute for Health Research

CANCER RESEARCH UK

UCL
LESSONS FROM RESEARCH (all ART children not just post PGD)

- Multiple pregnancies are the biggest risk
- Increased risk of pre term delivery
- Increased risk of peri-natal mortality
- Increased risk of SGA
- Increased risk of congenital anomalies
- Increased risk of some rare epigenetic abnormalities

Wednesday, 27 September 2017
Lessons from research

- Neurodevelopmental risks - no certain evidence of an effect.
- Increased risk of cerebral palsy (via LBW and multiples.)
- Psycho social development is normal.
- No increased risk of childhood cancer.
Final Message

- ‘Please think of the children’
- ‘Prima di tutto pensa ai bambini’
- ‘Denk aan de Kinderen alstublieft’
- ‘Lutfen cocuklari dikkat!’
- ‘Porfavor pensad en los ninos’
Questions

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- www.alastairsutcliffe.co.uk