Evaluating the Impact of IVF on Child Health Outcomes

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Works in Progress 15 December 2014

Supervisors: Prof. Daniel Brison, Dr. Stephen Roberts & Dr. Edward Johnstone
Examine the impact of ART on early human embryo development, pregnancy outcomes and health of offspring from perinatal life to early adulthood.

- International research consortium funded by the European Commission
- EU FP7 Consortium grant – Prof Daniel Brison, Dr Steve Roberts, Dr Sue Kimber
- Research Associates – Dr Helen Smith & Dr Mark Hann
- Three year Marie Curie Initial Training Network grant
- Employed as uni staff: Early Stage Researcher
“We now know that poor fetal growth and small size at birth are followed by increased risk of coronary heart disease, stroke, hypertension, Type-2 diabetes, and osteoporosis.”

- David J. P. Barker, 1995

- **Theoretical framework**: emphasizes the vulnerability and long-term influence of the very early stages of life including the pre-implantation and perinatal periods of development

- **Epigenetic re-programming**: translation of external influences on the maternal environment into adaptive responses in embryonic and fetal development during peri-conception period
  - Via regulation and/or dysregulation of gene expression → manifested as phenotypic characteristics

- Birth weight is a routinely collected proxy for fetal growth at birth.
Impact of IVF

> Five million IVF-conceived babies born worldwide

IVF accounted for ~2% of all live births in England and Wales in 2010 (ONS, 2011).

As of 2012: 77 clinics providing IVF treatments in the UK
- Initiated 60,471 cycles undergone by 48,387 patients in 2011
- Number of IVF cycles increased by 3.4% in 2010 and 7% in 2011
- Live birth rate per cycle increased from 14% in 1991 to 25% in 2011
- Number of IVF/ICSI cycles resulting in a live birth event in 2011: 14,567 (HFEA, 2013)

The majority of IVF-conceived singletons are born healthy.

Outside of multiple births, IVF conceived singletons are still at increased risk of detrimental neonatal outcomes compared to SC singletons.
Post-natal Health Outcomes of IVF Offspring

**IVF vs. Spontaneously Conceived Offspring**

- Increased risk of stillbirth & neonatal death (Pinborg 2010, Marino 2014)
- Lower average birth weight within normal bounds (Henningsen 2011)
- Increased rates of LBW and PTD (Schieve 2002, Henningsen 2011, Camarano 2012, Frangez 2014, Marino 2014)
- Increased rates of chromosomal and musculoskeletal birth defects (Hansen 2002)
- Gene expression differences found in placenta and cord blood (Katari 2009)

**IVF: Longer-term Outcomes**

- Cardiac characteristics (Valenzuela-Alcaraz 2013)
- Increased central, peripheral and total adiposity in pubertal girls (Belva 2012)
- Increased blood pressure & fasting glucose levels in children (Ceelen 2008)
IVF: Pre-implantation Environmental Influences

Kondapalli & Perales-Puchalt; Fertility and sterility 99.2 (2013)
Post-natal Health Outcomes of IVF Offspring

Fresh vs. Frozen-thawed

- **Fresh** born smaller than frozen (Pinborg 2010, Henningsen 2011, Kato 2012, Nakashima 2013); accelerated catch-up growth & more favourable lipid profiles in childhood (Green 2013)

- **Frozen**: Reduced rates of LBW (Kalra 2011), PTD (Pinborg 2010), and SGA (Pelkonen 2010) but *increased* rates of LGA (Ishihara 2014, Pinborg 2014), macrosomia (Marino 2014) and perinatal mortality (Wennerhold 2013).

Blastocyst vs. Cleavage Stage ET

- Blastocyst: increased rate of PTD (Dar 2013, Kalra 2012), increased risk of LGA (Ishihara 2013).

Culture Medium Effect

- Birth weight differences between Cook & Vitrolife culture media (Dumoulin 2010, Nelissen 2012); other studies found no differences between other media (Eaton 2012, Vergouw 2012)

Oestrogen levels during treatment

- **Fresh cycles**: increased incidence of FGR, placenta previa, pregnancy-induced hypertension (Farhi 2010), SGA & PreE (Imudia 2012/2013)
Post-natal Health Outcomes of IVF Offspring

- If increased long term health risks do result from IVF, then causal factors and extent to which they are modifiable to be robustly investigated

- Previous studies have been unable to account for many important confounders.
  - Multiple confounders/mediators must be unravelled

- Additional evidence is needed:
  - Detailed laboratory & clinical data
  - Across multiple centres and multiple time periods to capture differences in practice
Post-natal Health Outcomes of IVF Offspring

- **Hypothesis:** variation in IVF procedure practices is associated with corresponding differences in birth weight outcomes.

- **Aims:**
  - Investigate how standard practices in treatment have changed over time and how changes relate to birth weight outcome trends
  - Examine how up to date treatment standards vary between clinics and account for this variation over time
  - Identify the most influential laboratory procedures, reagents or treatment factors associated with birth weight differences
Post-natal Health Outcomes of IVF Offspring

All UK IVF Procedures

Year

1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013

Number of Sites

1
5
77

Data-rich

Data-limited
SMH 20 Year Data

HFEA Historical Returns: data from all cycles resulting in a Live Birth between 1992 and 2013

- All available **treatment, patient registration** and **live birth outcome** data reported to the HFEA by the St Mary’s Hospital Department of Reproductive Medicine over the last two decades

### Patient Factors:
- Cause of Infertility
- Parity and IVF Treatment History
- Ovarian Reserve
- Ethnicity
- Parental Age
- Post Code (SES)

### Treatment Factors:
- Fertilisation Method (IVF/ICSI)
- Cycle Type (Fresh/Frozen)
- Ovarian Stimulation Drugs Used
- Time in Culture
- Number of Embryos Transferred

### Birth Outcomes:
- Birth Weight
- Multiplicity
- Gestational Age
- Gender
- Fetal Reduction
- Congenital Anomalies
# SMH 20 Year Data

## Data Collection Issues
- Data collation problems:
  - 51,370 individual HFEA forms
- 3,096 Outcome Forms
  - Large amount of missing data after extraction and collation
  - 72% missing mother info
  - 75% missing paternal info
  - 24% missing treatment info
  - Individual form fields missing

## Future Plans
- New approach to raw data collation (yesterday)
- Determine whether extraction method is inadequate or HFEA data incomplete
- BW validation for those born at SMH (CMIS) – 20-23% in 2012
- Possible linkage with CPRD: parent health history linked to child health
Post-natal Health Outcomes of IVF Offspring

All UK IVF Procedures

Year
- 1991: Data-limited
- 1992: Data-limited
- 1993: Data-limited
- 1994: Data-limited
- 1995: Data-limited
- 1996: Data-limited
- 1997: Data-limited
- 1998: Data-limited
- 1999: Data-limited
- 2000: Data-limited
- 2001: Data-limited
- 2002: Data-limited
- 2003: Data-limited
- 2004: Data-limited
- 2005: Data-limited
- 2006: Data-limited
- 2007: Data-rich
- 2008: Data-rich
- 2009: Data-rich
- 2010: Data-rich
- 2011: Data-limited
- 2012: Data-limited
- 2013: Data-limited

Number of Sites
- 1
- 5
- 77
NOERG Collaboration Study

**Motivation**

- Need for large **multi-centre** samples: variation in patient populations and standard treatment protocols to test hypotheses suggested in literature
- Robustly test potential relationships between IVF treatment factors and child health outcomes
- Collection and collation of **laboratory procedure factors, patient characteristics**, and **birth outcome** data from 2007 to 2013
  - Including clinical data already reported to the HFEA
  - Additional data routinely recorded in electronic databases

Investigate relationships between influential treatment factors and birth weight
NOERG Collaboration Study

Led by members of the North of England Reproductive Medicine Group

- Central Manchester University Hospitals NHS Foundation Trust (*Dept. of Reproductive Medicine*)
- Leeds Teaching Hospitals NHS Trust (*Centre for Reproductive Medicine/Seacroft Hospital*)
- Liverpool Women’s NHS Foundation Trust (*Hewitt Fertility Centre*)
- Manchester Fertility Services (*Cheadle Hulme, Manchester*)
- Sheffield Teaching Hospitals NHS Foundation Trust (*Jessop Fertility*)
### Patient Information

**LEEDS** | **LIVERPOOL** | **MFS** | **CMFT** | **Sheffield**
---|---|---|---|---
Parental Age | | | | |
Infertility Diagnosis | | | | |
Infertility Duration | | | | |
IVF Attempt History | | | | |
Parity | | | | |
BMI | | | | |
Pre-existing Health Conditions | | | | |
Post code (SES) | | | | |
Ethnicity | | | | |
Lifestyle (e.g., smoking, alcohol) | | | | |

### Treatment Information

**LEEDS** | **LIVERPOOL** | **MFS** | **CMFT** | **Sheffield**
---|---|---|---|---
Stimulation Type | | | | |
Num Oocytes Used | | | | |
Num Embryos Created | | | | |
Fertilisation Type (IVF/ICSI) | | | | |
Cycle Type (Fresh/Frozen) | | | | |
Num Embryos transferred | | | | |
Dates of Mixing/Transfer | | | | |
Num Oocytes Retrieved | | | | |
Course of hormone treatment (e.g., peak oestrogen level) | | | | |
Sperm quality/morphology | | | | |
Embryo morphology | | | | |
Dates of Freezing/Thawing | | | | |
NOERG Collaboration Study

Time-dependent Treatment Factors

- Culture Medium Type
- Incubator Type (Culture Conditions)
- OHS Protocol Criteria

Widespread correspondence in collection of patient information, treatment data and incubator type use across clinics

Less overlap in Culture Media Use over time:

Changes in Culture Media by Clinic

- Leeds
- Liverpool
- MFS
- CMFT
- Sheffield

Additional centres that have used 2+ of the media represented are needed.
## NOERG Collaboration Study

### Post-natal Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LEEDS</th>
<th>LIVERPOOL</th>
<th>MFS</th>
<th>CMFT</th>
<th>Sheffield</th>
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<td>Birth Weight</td>
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<td>Gestational Age</td>
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<td>Gender</td>
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<td>Multiplicity</td>
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<td>Placental Weight</td>
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<td>Additional Baby Size Parameters</td>
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<td>Admission to NICU</td>
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Post-natal Health Outcomes of IVF Offspring

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Data-rich

Data-limited
National Culture Media Questionnaire

Led by Prof Joyce Harper & Prof Daniel Brison
University College London – The University of Manchester

Aim: examine the relationships between culture media and IVF success rates & birth weight

- Survey Data Collection:
  - All 77 licenced UK Infertility Clinics

- Patient Population:
  - IVF/ICSI Patients using their own gametes for fresh cycles

- Questionnaire Data:
  - Medium Name
  - Dates of Use
  - Stages Used for
  - Patients Used for
  - Embryo Transfer Dates

- Linkage with HFEA Data:
  - Number of Live Births
  - Fetal Hearts Seen
  - Multiplicity
  - Birth weight, Gestational Age, Gender
  - Parity & Pregnancy History
  - Parental Age
  - Number of Embryos Transferred
  - Infertility Diagnosis & Duration
  - Fertilisation Type (IVF/ICSI)
Thank You.

Supervisors
Prof. Daniel Brison
Dr. Steve Roberts
Dr. Edward Johnstone

Advisor
Dr Rosanne McNamee

Maternal & Fetal Health Research Centre team
Thank You.

St. Mary’s Hospital IVF Unit Team
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