Evaluating the Impact of IVF on Child Health Outcomes

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What is IVF?

- IVF: most invasive form of ART for the treatment of male & female infertility
- Following ovarian hyper-stimulation, process by which eggs are removed from ovaries and mixed with sperm in a laboratory environment where fertilization takes place in a culture dish
  - Majority of Standard IVF patients treated for unexplained infertility
  - Majority of ICSI patients treated for male factor infertility
- The first “test tube baby,” Louise Brown, was born in 1978 in Oldham, England.
- Over Five million IVF-conceived babies born worldwide since
Impact of IVF

- 1 in 7 heterosexual couples in the UK affected by infertility
- 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)
- Multiple births are the biggest single risk from IVF, but decreasing.

However, IVF conceived singletons are still at increased risk of detrimental neonatal outcomes compared to naturally conceived.
Post-natal Health Outcomes of IVF Offspring

**IVF vs. Spontaneously Conceived Offspring**

- Increased risk of stillbirth & neonatal death (Pinborg 2010, 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)
“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

- **Fetal Programming Hypothesis**: 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 the 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.
Developmental Origins of Health & Disease

Environmental Influence

Epigenetic Response to Environment

Occurring from around the time of conception and throughout fetal development

Adaptive Phenotype At Birth and Beyond

- Birth weight as a measure of child health at birth.
IVF: Long-term Pre-implantation Environmental Influences

IVF Treatment Factors

- Number of Embryos Transferred
- Duration of Culture
- Culture Medium/Environment
- Parental Characteristics/Subfertility
- Ovarian Stimulation/Cryopreservation

Embryo Quality

- Vanishing Twin

Implantation Potential

Embryo Development/Characteristics

Endometrial Quality

Suboptimal Implantation

Placental Deficiency

Post-natal Health Outcomes

Adapted from Kondapalli & Perales-Puchalt; Fertility and sterility 99.2 (2013)
IVF: Long-term Pre-implantation Environmental Influences

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Birth Weight?

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

- If increased long term health risks do result from IVF, can we identify causal factors and modify them?
- Previous studies have been unable to account for many important confounders.
  - Multiple confounders/mediators must be unravelled

**Hypothesis:** variation in IVF treatment 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 current treatments vary between clinics and investigate if these differences in practice relate to birth weight outcomes
- Identify the most influential laboratory procedures, reagents or treatment factors
Post-natal Health Outcomes of IVF Offspring

All UK IVF Live Birth data reported to the HFEA since 1991

Number of Clinics

1991-2013

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:**
  - Culture medium
  - Dates of use
  - Stages used for
  - Embryo transfer dates

**Linkage with HFEA Data:**
- Birth outcomes, treatment factors & patient factors

**Progress:**
- Designed & disseminated survey to all clinics
- Collaboration with Association of Clinical Embryologists & HFEA
Saint Mary’s Hospital 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

Progress

- Data request to HFEA: 50,000 individual treatment forms
- Designed R program to collate forms
- Data set consisting of:
  - ~2,617 patients
- ~2,816 live birth events
  - 2,329 singletons
  - 449 sets of twins
  - 38 sets of triplets
- Data cleaning and validation in progress

Future Plans

- Examine how changes in practice relate to birth weight trends over the study period. Examples:
  - Culture Medium Type
  - Oxygen Concentration
  - Embryo Freezing
- BW validation for those born at SMH (CMIS) – 20-23% in 2012
Post-natal Health Outcomes of IVF Offspring

All UK IVF Live Births Since 1991

SMH 20 Year Data

Data-rich

NCMQ

Number of Clinics

1 5 77
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** (*Cheadle Hulme, Manchester*)
- **Sheffield Teaching Hospitals** NHS Foundation Trust (*Jessop Fertility*)

*Mix of NHS and private treatment centres*
NOERG Collaboration Study

- Exploit differences in practice across clinics and over time
- Collection and collation of treatment procedure, patient and birth outcome data from 2007 to 2013
  - Including clinical data routinely reported to the HFEA
  - Additional data routinely recorded in electronic databases
- All sites have key variables available electronically
  - Metadata has been collected
  - Current overlap in Culture Media Use over time:

![Changes in Culture Media by Clinic](chart.png)
NOERG Collaboration Study

Progress

- Data sets collected:
  - SMH Manchester
  - Liverpool Women’s Hospital
- Data cleaning & validation in progress

Future Plans

- Addition of 2-3 additional clinics
  - 2 in recruitment
- Collation of separate datasets into single large multi-centre dataset
- Analyse independent effects of influential treatment factors on adjusted BW:
  - IVF/ICSI
  - Embryo Freezing
  - Ovarian Stimulation
  - Duration of Culture
  - Culture Conditions (medium/oxygen concentration)
Summary

Progress & Progression

- **NCMQ**: survey circulated to all clinics in the UK → responses coming in
- **SMH 20 Year Data**: data set collated → to be cleaned & validated
- **NOERG**: data sets being collected → cleaning and validation as they are collected

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Questions?
Thank You.

Supervisors
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Supporting Organizations
EpiHealthNet
Central Manchester University Hospitals NHS Foundation Trust
Maternal & Fetal Health Research Centre

NOERG Collaborators
Jessopfertility
Leeds Centre for Reproductive Medicine
Liverpool Women’s NHS Foundation Trust
Manchester Fertility

NCMQ Collaborator
UCL