Paediatric Endocrinology Research at Royal Hospital for Children and Young People (RHCYP), Edinburgh

RHCYP provides tertiary clinical services in paediatric endocrinology for Edinburgh and South-East Scotland with outreach to Dumfries and Galloway, Fife, Dundee and Highland. The team has a major clinical and research focus on reproductive endocrinology and contributes to multicentre UK research activities and clinical trials.

Paediatric Endocrinology Consultant Team:
Dr Louise Bath (Clinical Lead) – louise.bath@nhslothian.scot.nhs.uk
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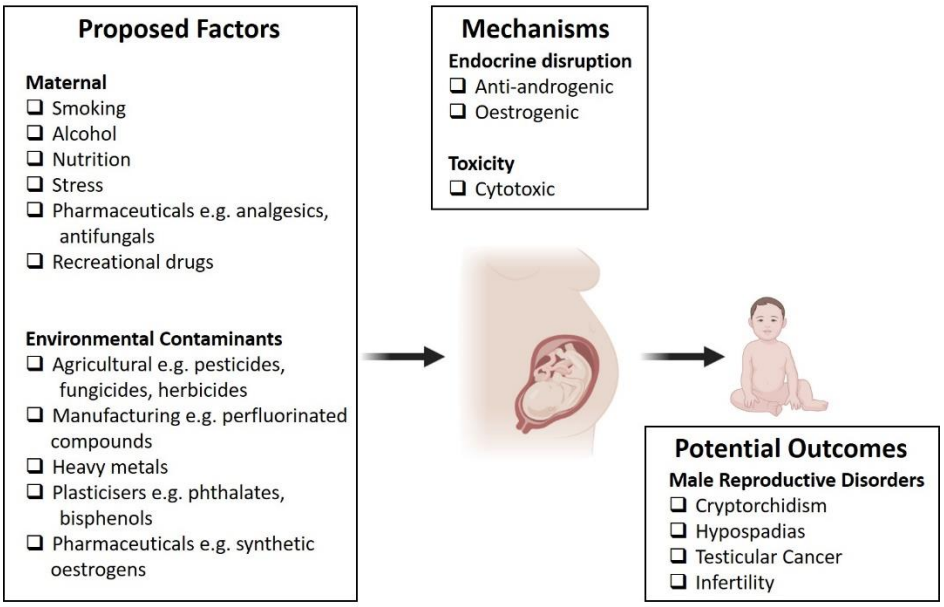
Dr Tarini Chetty – tarini.chetty@nhslothian.scot.nhs.uk
Prof Rod Mitchell – rod.mitchell@nhslothian.scot.nhs.uk (clinical); rod.mitchell@ed.ac.uk (research)

Research

1) Genetic and Environmental Impacts on Male Reproductive Development and function



The Edinburgh team have an international reputation in the role of genetics and environmental impacts on male reproductive development. This includes studies investigating the impacts of proposed Endocrine Disrupting Chemicals (EDCs) and pharmaceuticals on fetal and prepubertal testicular development and function. This includes the use of human-relevant experimental model systems to explore the impacts and mechanisms behind male reproductive disorders.

Our main areas of research in this area:

1) Impacts of exposure to EDCs on human fetal testis development.

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2) In-vitro systems for genetic manipulation of human fetal testis to model 'testicular dysgenesis' and DSD.
3) Impacts of exposure to pharmaceuticals (e.g. analgesics, antifungals) on steroidogenesis and germ cell development in human fetal testis.

Research tools:

1) In-vitro culture system for human fetal testis development and function. The system can be used to monitor short term effects of 'human-relevant' exposures on endocrine function (testosterone, Inhibin B, AMH), testicular development and germ/somatic cells in human fetal and prepubertal testis.
2) Ex-vivo (xenograft) model to investigate long-term impacts of exposure on human fetal testis tissues.
3) Single-cell sequencing of human fetal testis (+/- exposures).
4) Maternal and Neonatal Registry Databank (>150000 pregnancies). Aberdeen Maternity Hospital including pharmaceutical exposure data.

Specific studies:

1) Impact of paracetamol and ibuprofen on human fetal testis development and function.
2) Role of genes implicated in DSD (e.g. DMRT1 and DHX37) in the development of testicular dysgenesis.
3) Role of the placenta in modulating EDC effects on testicular development and function.

Researchers within the group:
Professor Rod Mitchell (Lead)
Dr David Greenald

Supporting consultants:
Dr Tarini Chetty
Dr Harriet Miles

Internal collaborations: Obstetrics and Reproductive Health (Professor Richard Anderson), Paediatric Oncology (Professor Hamish Wallace, Dr Mark Brougham)

External Collaborations: Endocrinology in Karolinska (Stockholm; Olle Soder and Jan-Bernd Stukenborg), Paediatric Oncology (Oxford; Sheila Lane), Reproductive Biology (Aberdeen; Paul Fowler), Rigshospitalet (Copenhagen; Anne Jorgensen), University of Pittsburgh (Pitsburgh; Jennifer Adibi)

5-year Vision for Male Reproductive Development studies in Edinburgh:
We will continue our work on pharmaceutical exposures in human fetal testis focusing on pharmaceutical exposures and impacts on steroidogenesis and germ cell development. We will also continue collaborations exploring clinical data registries exploring associations between pharmaceutical exposures and reproductive outcomes in offspring of exposed mothers. We will also develop our collaboration exploring the role of the placenta in modulating endocrine disruption (phthalate exposure) in the human fetal testis through an NIH-funded project (2018-2022).

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2) Fertility Preservation in Children with Cancer

The Edinburgh team are leaders in the field of fertility preservation in prepubertal boys and girls (www.ed.ac.uk/edinburgh-fertility-preservation). The programme for female fertility preservation has been ongoing for >20 years, whilst the first UK clinical research programme for males was established in Edinburgh in 2015. The programme involves ovarian and testicular biopsies prior to gonadotoxic treatment, with storage of tissue for future clinical use. This is combined with a research programme that combines laboratory-based experimental studies aimed at understanding how cancer treatment affects the gonads and methods to preserve and restore fertility, with a clinical programme of patient follow-up to determine patient outcomes.

Our main areas of research in this area:

1) Effects of cancer treatments on human prepubertal testis.
2) Developing strategies to prevent gonadotoxic damage in the testis.
3) Restoration of fertility through in-vitro spermatogenesis or testicular tissue transplantation.

Research tools:

1) In-vitro culture system for prepubertal human testis development and function. The system can be used to monitor short term effects of 'human-relevant' chemotherapy exposures (+/- 'chemoptotectants') on germ/somatic cells in human prepubertal testis.
2) Ex-vivo (xenograft) model to investigate long-term impacts of chemotherapy exposures (+/- 'chemoptotectants') on human prepubertal testis tissues.
3) Single-cell sequencing of human prepubertal testis (+/- exposures).
4) Nanoparticle tracking analysis to investigate role of extracellular vesicles in chemotherapy-induced testicular damage.
5) High-throughput drug screening approach to identify compounds that can protect from chemotherapy-induced testicular damage.

Specific studies:

1) Testicular tissue cryopreservation for fertility preservation in children receiving gonadotoxic therapies includinf long-term follow-up of reproductive function (puberty, Leydig cell function and fertility).
2) Impact of platinum-based chemotherapy on germ and somatic cells in human prepubertal testis.
3) Testicular transplantation of prepubertal testis tissues to promote spermatogenesis.

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4) Extracellular vesicles as mediators for (or protection from) chemotherapy-induced testicular damage.

Researchers within the group:
Professor Rod Mitchell (Lead)
Professor Richard Anderson
Professor Norah Spears
Dr Federica Lopes
Dr David Greenald

Supporting consultants:
Professor Hamish Wallace (Paediatric Oncology)
Dr Mark Brougham (Paediatric Oncology)
Dr Phil Hammond (Paediatric Surgery)
Dr CJ Shukla (Urology)

Internal collaborations: SNBTS (Sharon Zahra)

External Collaborations: Endocrinology in Karolinska (Stockholm; Olle Soder and Jan-Bernd Stukenborg), Paediatric Oncology (Oxford; Sheila Lane); Reproductive Biology (Brussels; Ellen Goossens), (Amsterdam UMC; Ans van Pelt), Andrology (Muenster; Stefan Schlatt) and Urology (London UCL; Pippa Sangster).

5-year Vision for Fertility Preservation studies in Edinburgh:

We will continue our research exploring the impacts of human-relevant chemotherapy exposures on prepubertal human testis and to develop clinical options for prevention of gonadotoxicity or restoration of fertility. This work is currently supported by UKRI (2019-2024). We will utilise ongoing collaborations to create a UK registry for fertility preservation in children and young adults. We will continue to promote fertility preservation in this age-group through ongoing collaborations for research and clinical activity and continued publication national and international published guidelines.

3) Contribution to UK Multicentre Research Studies

In addition to the work on fertility preservation and male reproductive health, RHCYP plays an active role in several ongoing multicentre research studies:

1) BPSU - Unexpected Adrenal Suppression Study - Lead for Scotland – Dr Harriet Miles

2) Closed-Loop Diabetes (CLOuD) study – Lead for Scotland – Dr Daniela Elleri

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