# 2018 MPhil Vignettes in Women’s and Children’s Health

(Some of these vignettes can also be incorporated into MRes studentships; please contact the relevant supervisor for more information)

## Table of Contents

### Child Health

1) Paediatric Clinical Pharmacology
   - The risks and benefits of Valproate therapy in female paediatric patients (Hawcutt) ............................................ 2
   - Management of acute severe asthma in children (Hawcutt/Sinha) ............................................ 2
   - Developing personalized use of anti-retroviral therapies for bronchiolitis (Hawcutt/McNamara) ............. 3
   - Adverse drug reactions in children with neuro-disability (Hawcutt) ............................................ 4
   - Development of a handover tool to improve information about research patients and reporting of suspected ADRs (Hawcutt) ................................................................................................................................. 4

2) Paediatric Surgery
   - Regenerative Medicine Therapies in Acute Kidney Injury (Kenny) ............................................ 5

3) Paediatric Rheumatology and Renal Medicine
   - Investigating the pathogenesis of Lupus Nephritis in Juvenile SLE (Wright/Beresford) ............ 6
   - The molecular pathophysiology of Chronic Nonbacterial Osteomyelitis (Hedrich) ...................... 7
   - Drug-induced kidney injury in children (McWilliam) .................................................. 8

4) Neurodevelopmental Paediatrics
   - Examining and measuring neurodevelopmental outcomes in infants and children affected by prematurity or infections in global health or UK settings (Gladstone) .................................................................................................................. 9

5) Paediatric Respiratory
   - Predicting disease severity in infants with bronchiolitis (McNamara/Flanagan/van Miert/Saint) .... 10
   - Evidence based medicine in outpatient paediatric asthma (Sinha/Nolan/Hawcutt) .................... 10
   - Liverpool Baby Breathing Study (Semple) .................................................................................. 10
   - Systematic Review of an intervention for CF (Southern/Sinha) ............................................ 11

6) Neonatology
   - Brain function during transitional circulation in preterm infants (Turner) ........................................... 12

### Women’s Health

1) Obstetrics
   - Clinical trials of postpartum haemorrhage management (Weeks) ..................................................... 13

2) Gynaecology
   - Developing a 3D model for embryo-endometrial interaction (Hapangama) ........................................ 14
   - Examination of Telomerase associated proteins in endometriosis and endometrial cancer (Hapangama) .................................................. 14
   - An exploratory Study aiming to explain why women menstruate? (Hapangama) .................... 14
   - Examination of the epithelial stem cell marker Lgr5 in endometriosis (Hapangama) .................. 15
   - Examination of NMR metabolomics to develop new, non-invasive diagnostic strategies in endometriosis and endometrial cancer (Hapangama/Phelan) .................................................................................................................. 15
**1) Paediatric Clinical Pharmacology**

**a. The risks and benefits of Valproate therapy in female paediatric patients (Hawcutt)**

There is considerable controversy about the effects of valproate on unborn babies, with recent data suggesting that up to 40% of children have long term effects including learning difficulties and neurodevelopmental issues. This makes the case for adult women clear, but it is less clear how the risks and benefits can be assessed in pre-pubertal and teenage girls. The MPhil would encompass:

- Systematic review of the evidence of benefits and harms in pre-pubertal and peri/post-pubertal female patients prescribed valproate for seizures. We have links with support charities for parents of children affected by Valproate in utero, and we will work on establishing the most important outcomes with them. This is a very important study, that may affect the use of valproate in seizures nationally and internationally.

- Depending on the time taken for the systematic review (which is the primary goal of the MPhil), there may also be opportunity to participate in adverse drug reaction research related to the use of anti-epileptic medications in children.

*Contact Dan Hawcutt (dhawcutt@liverpool.ac.uk) for more information*

**b. Pharmacogenomics of theophyllines in chronic severe asthma (Hawcutt/Sinha)**

Theophylline is metabolised by CYP1A2, a gene with known polymorphisms that have been described as affecting function (clearance of caffeine for example in some populations). It is used in the treatment of chronic asthma, but inter-individual variation in the concentration achieved following dosing is large. The MPhil (or MRes if divided up into 3 segments) would encompass:

- Systematic review of the evidence for i) dose and ii) therapeutic range of theophylline when used orally for chronic severe asthma in children and young people. We have successfully published previous systematic reviews from MPhil students, and developed new systematic review methodologies which we have published (and will use here).

- Design and implement (including patient recruitment) a new arm of the MAGIC study (a pre-existing multicentre study that collects DNA from children who have therapeutic drug monitoring undertaken or adverse drug reactions) to recruit children using oral theophylline

- Candidate gene analysis (including laboratory based DNA extraction and analysis in the Wolfson centre for Personalised medicine) will be undertaken of children and young people recruited to the MAGIC study to compare dose of theophylline, levels achieved, and CYP1A2 status.

*Contact Dan Hawcutt (dhawcutt@liverpool.ac.uk) for more information*
c. Management of acute severe asthma in children (Hawcutt/Sinha)

Although there are several different intravenous medications to manage children with acute severe asthma, there are numerous unanswered questions regarding the optimum management. This MPhil will build on previous successful work that led to peer reviewed publications for the MPhil student. The MPhil (or MRes if divided up into 3 segments) would encompass:

a) Systematic review of the scoring systems used to work out how unwell children are with acute severe asthma. This would be submitted for publication
b) Design and implement the most appropriate asthma severity score to the current A&E documentation in Alder Hey Children’s Hospital to improve patient care directly. Prospectively audit the completion of this updated documentation to assess the accuracy and completeness of completion (to see if it actually works). This would be submitted to conferences in the UK and considered for publication.

c) Continue to recruit to a pharmacogenomics study of iv aminophylline in acute asthma (part of the MAGIC study – already has ethical approval and is recruiting in the UK) to undertake a candidate gene analysis of aminophylline levels and CYP1A2 status (incorporating previous data from MPhils)

Contact Dan Hawcutt (dhawcutt@liverpool.ac.uk) for more information

d. Developing personalized use of anti-retroviral therapies for bronchiolitis (Hawcutt/McNamara)

Multiple anti-retroviral agents are in the late stages of development for infants with RSV+ bronchiolitis. These have the potential to drastically reduce hospital admission, but will be very expensive medications. It is therefore necessary to develop a system to assess infants early in the disease (in primary care) that can distinguish between those who are likely to deteriorate and those who are likely to remain well. Clinical data exists that can stratify children into risk bands, but this has not been paired with new, validated scoring systems that can accurately assess the level of illness. Parental involvement with the design of such stratification systems is crucial, as well as public acceptance of them once developed.

Workstreams:

- Systematic Reviews of risk factors causing severe disease in RSV+ bronchiolitis (including, where available, size of effects) – including but not limited to smoking, prematurity, cardiac disease, age
- Pilot study of ability to use Validated Bronchiolitis score in Primary care situation – does this system work in this setting, how well do GPs, Practice nurses, and families accept it?
- Quantitative component – how many infants were assessable, who did it
- Qualitative component – did parents/GPs like it?
- Pilot study of stratification of infants into risk categories (using criteria established in systematic review) – with follow up to see how well the score does. Statistical analyses to establish the effect sizes of the risk factors identified and see if future pharmacogenomic
testing would be a useful adjunct (especially if clinical risk only a small percentage of the overall risk for a child).

Contact Dan Hawcutt (dhawcutt@liverpool.ac.uk) for more information

e. Adverse drug reactions in children with neuro-disability (Hawcutt)
Children with neuro-disability often take multiple medications, which is a major risk factor for adverse drug reactions (ADRs). However, they also have communication difficulties, making assessment of a potential adverse drug reaction more difficult than in another child of the same age with developmentally appropriate communication skills. This MPhil will look at several areas:

- Systematic review of Adverse Drug reactions in the neuro-disabled child (specifically, how many have been reported in the literature, how were they identified, what is the frequency, severity, etc). This will be paired with a review of existing (unpublished) database (ADRIC study) to establish which children (in a yearlong prospective study) with neuro-disability were suspected of having an adverse drug reaction, and descriptive analyses of the reactions suspected – this work is expected to be submitted for publication.
- Qualitative study looking at knowledge and understanding of ADRs amongst parents of children with neuro-disability, including How would they identify an ADR? What would they do if suspected an ADR? Do they know about Yellow Card App and Parental reporting?
- Causality assessment of suspected ADRs. There are validated tools to work out if a suspected ADR is likely to be caused by a drug. These have focussed on health professionals, but could be completed by parents. This phase of the work will pilot the assessment of the acceptability and ease of use of the Liverpool Causality tool in parents of children with neuro-disability.

Contact Dan Hawcutt (dhawcutt@liverpool.ac.uk) for more information

f. Development of a handover tool to improve information about research patients and reporting of suspected ADRs (Hawcutt)
There are many children in clinical trials within Alder Hey, some on the wards, and some on the specialist NIHR Alder Hey Clinical Research Facility. These children stay overnight, and their care is delivered by the on call team. The research will vary, but they may not have “standard” treatments, may have blinded medications, or specific reporting criteria for suspected adverse drug reactions. This MPhil will build on a recent systematic review and develop and implement a handover tool that also improves the documentation of ADRs. This will require input from patients, researchers, and ward staff, and will be written up for publication in a peer reviewed journal.

Contact Dan Hawcutt (dhawcutt@liverpool.ac.uk) for more information
2) Paediatric Surgery

a. Regenerative Medicine Therapies in Acute Kidney Injury (Kenny)

Acute kidney injury is a leading cause of morbidity and mortality following trauma, sepsis and surgery. This is an opportunity to undertake a project within an innovative and motivated team combining interests in cell biology, immunology and kidney disease in a multi-disciplinary team of surgeons and basic scientists.

We are investigating the effects of stem cell therapy in acute kidney injury, with a view to finding a therapy that will be translated into safe clinical use.

You will have the opportunity to be involved in a focussed research project which combines the use of novel imaging techniques for cell tracking with laboratory based analysis of the immune modulation that occurs with stem cell therapy. The focus of the project will include:

- Literature review regarding the immune function of the lungs after stem cell therapy.
- Laboratory analysis of lung tissue following stem cell delivery to examine for stem cell distribution, cell apoptosis and macrophage engagement.
- Correlation between the above findings and bioluminescence imaging to increase our understanding of the fate of stem cells after acute kidney injury.

You will work closely with a surgeon currently undertaking a PhD and you will be supported in learning a variety of lab-based techniques. Successful candidates will be to present their work at international conferences and publish in peer reviewed journals.

Contact Simon Kenny (simon.kenny@alderhey.nhs.uk) for more information
3) Paediatric Rheumatology and Renal Medicine

a. Investigating the pathogenesis of Lupus Nephritis in Juvenile SLE (Wright/Beresford)

Juvenile-onset systemic lupus erythematosus (JSLE) is a severe, systemic autoimmune disease, characterised by inflammation and organ damage. Up to 80% of UK children develop renal involvement, termed Lupus Nephritis (LN); a quarter of these develop permanent kidney damage.

Currently, early diagnosis of LN is difficult as routine clinical measurements may occur later in irreversible inflammatory renal process. With more accurate prediction of disease onset, severity, and treatment response, modified therapy could minimise drug side effects.

Clinicians use inflammatory markers, autoantibody levels, complement and urine protein quantity, along with clinical judgment and experience, to decide on whether to perform a renal biopsy in LN. The current clinical markers used to track and monitor LN disease activity are restricted. Therefore, there has been great interest in research looking at novel urinary biomarkers that could track disease activity.

The project will be integrated into an already established translational programme of research within the UK Juvenile-onset Systemic Lupus Erythematosus (JSLE) Cohort Study. The successful candidate will join a multi-disciplinary Paediatric Rheumatology Research team that are based in the Institute of Child Health at Alder Hey which is the only Centre of Excellence for Childhood Lupus and is the UK’s first and only “Experimental Arthritis Treatment Centre for Children” (EATC).

Our group has optimised 3 kidney cells lines – mesangial cells, glomerular endothelial cells and podocytes and these are essential for our understanding of glomerular kidney disease as these are the cell types most vulnerable to damage.

Alarmins are molecules that are usually sequestered within cells under homeostatic conditions however upon infection/tissue damage these are released into the extracellular environment where they act upon immune cells to induce/exacerbate inflammation. Alarmins are raised in the systemic circulation during active SLE and thus these may play an important role in the pathogenesis of LN. Those found to be of interest in the pathogenesis of JSLE include S100 proteins, HMGB1 and dsDNA; these will be investigated in the following project using samples from our UK JSLE Cohort.

This project will aim to investigate the role of alarmins in LN by:

- Performing a literature review on the current evidence of alarmins in juvenile LN
- Characterising the levels of alarmins in the serum/urine of juvenile LN patients compared to those without LN and healthy controls
- Treating kidney cell lines with identified alarmins and determine inflammatory cytokine/chemokine levels

As well as being involved in the recruitment and collection of fresh samples, the candidate will also have access to prospectively collected samples and detailed phenotypic data. After this project the candidate will be proficient in cell culture techniques, antibody staining, flow Cytometry, ELISA and qRT-PCR.
b. The molecular pathophysiology of Chronic Nonbacterial Osteomyelitis (Hedrich)
Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory bone disorder that primarily affects children and adolescents with a peak onset between 7 and 12 years. The clinical spectrum is variable and ranges from single asymptomatic bone lesions up to the most severe form of chronic recurrent multifocal osteomyelitis (CRMO). Due to this variable clinical presentation with sometimes rather mild and unspecific clinical symptoms, diagnosis is frequently delayed or even missed. This is particularly worrying, since untreated CNO may result in bone sclerosis, pathological fractures (mainly of the vertebral bodies) sometimes with subsequent neurological symptoms, growth anomalies, pain amplification, and psychosocial problems. Thus, CNO and CRMO can significantly influence the development and quality of life in affected individuals.

Recent discoveries contributed to a better understanding of underlying molecular mechanism leading to systemic inflammation in CNO. However, the exact molecular pathophysiology remains incompletely understood. To our current understanding, several molecular disturbances contribute to the molecular pathophysiology of CNO. Bone inflammation may be the result of dysbalanced cytokine expression (namely reduced expression of the immune regulatory cytokine IL-10, and increased expression of pro-inflammatory IL-1beta, IL-6, and TNF-alpha) from innate immune cells and subsequent osteoclast differentiation and activation, resulting in bone remodeling and inflammatory bone loss.

The project will be integrated into an already established translational programme of research within the University of Liverpool. The successful candidate will join a multi-disciplinary Paediatric Rheumatology Research team that are based in the Institute of Child Health at Alder Hey which is the only Centre of Excellence for Childhood Lupus and is the UK’s first and only “Experimental Arthritis Treatment Centre for Children” (EATC).

Our group has identified several molecular mechanisms contributing to cytokine dysregulation and pro-inflammatory immune cell phenotypes in CRMO. However, the exact effects of these alterations remain elusive and it is unclear why these alterations result (primarily) in bone inflammation and inflammatory bone loss in CNO/CRMO.

This project will aim to investigate the role of imbalanced cytokine expression in the pathophysiology of CNO/CRMO by:

- Performing a literature review on the current evidence of immune dysbalance and altered cytokine expression in autoinflammatory disease influencing bone density and structure.
- Characterizing monocytic cell lines (THP-1 cells) that are deficient of the immune regulatory cytokine IL-10 and testing their capacity to differentiate into macrophages or osteoclasts.
- Treating ex vivo isolated human monocytes (from CRMO patients and controls) with cytokines and blocking those in order to test their differentiation capacity into macrophages or osteoclasts.

Contact Rachael Wright (rdwright@liverpool.ac.uk) for more information
As well as being involved in the recruitment and collection of fresh samples, the candidate will also have access to prospectively collected samples and detailed phenotypic data. After this project, the candidate will be proficient in ex vivo isolation of immune cells, cell culture techniques, flow Cytometry, ELISA and qRT-PCR.

Contact Prof Christian Hedrich (chedrich@liverpool.ac.uk) for more information

c. Drug-induced kidney injury in children (McWilliam)

Drug-induced kidney injury is the second most common cause of Acute Kidney Injury (AKI) in all children, and the most common cause in children aged 6 and above. Almost a quarter of these children die before discharge, and survivors had significant renal morbidity and mortality, which affects them for the rest of their lives.

There are no published data quantifying drug-induced kidney injury in children in the UK. However, exposure to nephrotoxic medications, such as aminoglycosides, is common.

This project will seek to describe the epidemiology and outcomes of drug-induced kidney injury at Alder Hey Children’s hospital, to review the literature, and will lead to an intervention to reduce this preventable cause of morbidity and mortality.

The project will include:

1. A prospective audit of AKI at Alder Hey children’s hospital, assessing the contribution of nephrotoxic medications
2. Collection of outcome data on children following drug-induced kidney injury from Alder Hey’s electronic patient data system and electronic prescribing system.
3. Systematic review(s) of drug-induced kidney injury in children focussing on the most common nephrotoxic drugs identified in the audit
4. Design of a quality improvement project aiming to decrease the incidence of drug-induced kidney injury at Alder Hey.

We would expect the audit to be presented at national meetings in the UK and the data to be submitted for publication. The systematic review(s) would be submitted for publication. The quality improvement project will result in better care for children in the hospital and beyond.

For more information, please contact Dr Steve McWilliam, NIHR Academic Clinical Lecturer in Paediatric Clinical Pharmacology: stevemcw@liverpool.ac.uk
4) Neurodevelopmental Paediatrics

a. Examining and measuring neurodevelopmental outcomes in infants and children affected by prematurity or infections in global health or UK settings (Gladstone)

An MPhil in Neurodevelopmental paediatrics could include research into interventions to improve outcomes of those with neurodevelopmental disorders or delay in the UK or in low income settings. This could include studies looking at identification and screening for infants born prematurely or those who are at risk of developmental delay. We have conducted studies on the use of neurodevelopmental assessment tools, behavioural assessment tools, maternal child interaction measures and measures to assess participation and functioning of children with disabilities.

Our research group works on the feasibility of low cost interventions for parents of children with neurodevelopmental delay and disabilities both in low resource settings and within the UK. We are working closer with Liverpool Community Health and have conducted work looking at family centred approaches to care for children with neurodisabilities in Liverpool using parent feedback tools. We also have looked at the investigation and management of a range of neurodevelopmental disorders including ADHD and ASD in Liverpool as well as in low income settings in Africa.

This MPhil project could specifically look at the measurement of neurodevelopmental delay and disability in low income or UK settings. There also could be a focus of work relating to present studies being conducted in Zika virus infection globally or in other neurodevelopmental insults in low income settings.

A further study could be conducted on the present screening programmes conducted in Merseyside by health visitors who are using the Ages and Stages developmental screener to identify children with problems.

We have had previous Mphil students complete excellent qualitative studies in Liverpool relating to the care of children under the age of 2 (linked with the Liverpool Women’s Hospital NNU as well as Liverpool Community Health) both which have since been presented at national and international meetings and written up for publication. We will support the training for conducting qualitative studies, systematic reviews or quantitative work. We will also support the possibility of conducting research in a LMIC setting if feasible and funding available at the time.

Contact melglad@liverpool.ac.uk for more information
5) Paediatric Respiratory

a. Predicting disease severity in infants with bronchiolitis 
   (McNamara/Flanagan/van Miert/Saint)

Bronchiolitis is an acute respiratory condition of infancy, often caused by Respiratory Syncytial Virus (RSV). In the UK, it’s the 2nd commonest cause of paediatric medical hospitalisation after asthma. No specific cures are available and the mainstays of treatment remain supportive. Most infants recover quickly from this illness but there is a small proportion of those hospitalised who require intensive care. Unfortunately, we cannot predict which infants will deteriorate.

At Alder Hey, we have a long published track record of investigating RSV disease in children. Much of the morbidity associated with RSV bronchiolitis is due to the host immune response to infection and we were one of the first groups to carefully document this in the lungs of babies with severe disease. We were also first to highlight the importance of viral co-infection in bronchiolitis and its link to disease severity. More recently, as part of an NIHR funded clinical PhD-studentship, we have developed a clinical score to assess disease severity in infants with bronchiolitis.

The aim of this study is to combine our severity score with inflammatory markers in respiratory secretions to find out whether we can predict which infants will deteriorate in hospital. Ethical approval is already in place for you to undertake this study.

We are looking for enthusiastic medical students with enquiring minds. You will be spending time in the laboratory (don’t worry about this, we’ll teach you all the lab skills you’ll need to complete this project!) and on the wards seeing children with bronchiolitis and assessing their disease severity. It is expected that you will gain at least one publication in a high-impact journal from your studies and that you will present your findings at an international respiratory conference in either the USA or Europe. As a group, we have a track record of successfully bringing MPhil students through into AF, ACF and ACL posts.

For further detail, please contact Professor Paul McNamara (mcnamp@liv.ac.uk)

b. Evidence based medicine in outpatient paediatric asthma
   (Sinha/Nolan/Hawcutt)

This MPhil will involve a systematic review and meta-analysis of commonly used therapies in paediatric asthma (steroids and add-on therapies), and some work with parents and clinicians to identify how the results of this evidence should be presented to them to maximise the usefulness of the review

c. Liverpool Baby Breathing Study (Semple)

The Liverpool Baby Breathing Study is an ongoing prospective, longitudinal birth cohort study that uses the Liverpool Respiratory Symptom Questionnaire (LRSQ) to conduct a biannual assessment of the respiratory symptoms of preschool children in Liverpool from birth to the age of 5 years. The study uses contemporary information technology solutions to facilitate recruitment, consent and
longitudinal data collection. The study was approved by the National Research Ethics Committee on 8th of May 2012 (REC ref: 12/EM/0194).

This study aims to map the natural history of respiratory symptoms of preschool children born in Liverpool and the impact of these symptoms on family life. The impact on family life is a unique feature in this study.

**Primary Objectives:** To describe parent reported respiratory symptoms in a population based birth cohort followed longitudinally form birth to five years old using the LRSQ.

**Secondary Objectives:** To examine any association between differences in respiratory symptoms in groups of preschool children with different social and environmental risk and protective factors.

The study benefits from generous support from a parents and friends group. Four successful MPhil candidates have run with this study (Pickles, Griffiths, Patel, Stead) which is now entering the sixth and final year. There is a large body of data ready for longitudinal analysis.

The student will be supervised by Dr Calum Semple, Senior Lecturer in Child Health who is happy to discuss the project either in person at the Institute in The Park at Alder Hey, by email m.g.semple@liverpool.ac.uk or by skype (ID=maes_celyn)

d. **Systematic Review of an intervention for CF (Southern/Sinha)**

At the end of this year we will expect the student to:

- Publish a protocol on the Cochrane database
- Publish a full review on the Cochrane database
- Present these findings at an international CF Conference
- Review outcome measures that are pertinent in CF and define a core outcome set
- Be confident at searching for appropriate levels of evidence
- Be able to identify the potential sources of bias in clinical trials
- Be able to undertake a meta-analysis of data from several different studies

Supervisors for this MPhil will be Prof Kevin Southern and Dr Ian Sinha. Both supervisors have completed several Cochrane reviews and are actively involved in the CF and Genetics Disorders Cochrane Review Group, which is based at Alder Hey.

The project will focus on an intervention for the condition, Cystic Fibrosis.

For more information on this project contact Kevin Southern, kwsouth@liv.ac.uk
6) Neonatology

a. Brain function during transitional circulation in preterm infants (Turner)

Hypotension is one of the most prevalent diagnoses in preterm infants and is associated with increased risk of brain injury and adverse neurodevelopmental outcome later in life. The brain and the autonomic nervous system regulates the cardiovascular system and moreover the vasculature perfusing the brain. As brain dysfunction evolves the body enters a state of multiple organ failure due to poor overarching regulation by autonomic nervous system. The background physiology is further complicated in the clinical environment as hypotensive infants are treated with inotropic and sedation drugs with possible potent cerebral effects without strong background evidence.

The aim of this study is to investigate further the physiology and pathophysiology of brain function and injury during normal and abnormal adaptation using continuous non-invasive methods.

We aim to recruit babies less than 30 weeks. All vital signals (blood pressure (BP), heart rate, pulse oximetry, respiratory rate, HeRo score) will be downloaded in real time from the clinical monitors. When available, electroencephalographic and cerebral near infrared spectrometry (NIRS) data will also be collected. This will be used to assess autonomic function (variability of heart rate and other parameters) and, when available, cerebral autoregulation (BP-NIRS correlation and coherence), cerebral oxygenation and cerebral electrical activity. All the above biomarkers will be related to clinical outcomes consisting of the grade of intraventricular haemorrhage. An existing dataset will be extended to assess neurodevelopmental outcome at 2 years of age for a cohort that was built using similar methods. The project will build on existing ethics approvals and analytic procedures supplemented by the development of new methods.

For more information on this project contact Mark Turner: mturner@liverpool.ac.uk
Women’s Health

1) Obstetrics

a. Clinical trials of postpartum haemorrhage management (Weeks)

Post-Partum Haemorrhage (PPH) is a common maternity emergency affecting 40,000 women across the UK each year. The incidence and severity of PPH is increasing and novel treatments are urgently needed. The most common cause is failure of the womb to contract, and drugs are first administered to cause contraction. If these fail, then the woman is taken into an operating theatre to find the source of the bleeding, and physical methods used to stop the bleeding under anaesthetic. A device that could simply ‘turn off the tap’, without the need for surgical intervention, would be a major advance in PPH management.

The PPH Butterfly is a completely new device. It is placed into the birth canal when bleeding starts and allows the doctor or midwife to stop the bleeding by squeezing the womb against it. It also detects whether the bleeding is coming from the womb or vaginal tears. The NIHR i4i programme has funded the design and initial human testing of the device. In the new study, the effectiveness of the device will be assessed in an observational study of 118 women with PPH at Liverpool Women’s Hospital. Interviews will be conducted with staff and recruited women to assess the device’s acceptability and usability. A health economics analysis will look at the costs of a PPH when managed traditionally, and when treated by the PPH Butterfly. Cost and clinical outcome data from recruited women will be compared with that of a historical cohort. A large research team has been assembled to conduct this study. Within the team, the MPhil student will:

- Assist in the conduct of the observational study. This means ensuring that the clinical and research governance is in place for the study (including ethical approval), ensuring that supplies of the device are widely available and that doctors have all been trained in its use, collecting study forms and entering the data onto a database, working with the study team to ensure that participants and users are interviewed in a timely fashion following the study.

- Be responsible for analysing the matched historical data. This will be the student’s primary responsibility. For every woman recruited to the study a woman with PPH from exactly one year previously will be identified who matches the recruit for parity and type of delivery. Her outcomes will be recorded and compared to those of the recruited woman.

The data will be compiled and analysed by the student. The report will form part of the final output for the study and the student will be on the authorship of the main paper reporting the observational study. In addition, if time allows, the student will have the chance to analyse overall trends in PPH rates at Liverpool Women’s Hospital with view to publication of the data.

Contact aweeks@liverpool.ac.uk for more information
2) **Gynaecology**

a. **Developing a 3D model for embryo-endometrial interaction**  
(Hapangama)

Embryo-implantation is the ultimate function of the endometrium. Endometrial receptivity accounts for over 70% of implantation failures but our current understanding of this process is deficient. Due to the unique nature of embryo-endometrial interaction in the human, animal models are not suitable. We therefore planning to develop an in-vitro 3D model using human cell lines initially to simulate human implantation in collaboration with scientists at the Karolinska institution in Sweden and Aston University Birmingham. Cell culture (2D and 3D) and advanced molecular techniques will be employed.

*Supervisor: D Hapangama*

*Contact email: dharani@liv.ac.uk*

b. **Examination of Telomerase associated proteins in endometriosis and endometrial cancer** (Hapangama)

Eukaryotic chromosomal ends are linear and are protected by nucleoprotein complexes known as telomeres. The complex structural anatomy and the diverse functions of telomeres as well as the unique reverse transcriptase enzyme, telomerase that maintains telomeres are under intensive scientific scrutiny. Both are involved in many human diseases including cancer. Their intricate involvement in many cellular processes and pathways is being dynamically deciphered in many organs including the endometrium. Our recent work has highlighted for the first time that telomerase is vital for normal endometrial regeneration and epithelial proliferation. Since telomerase is pivotal to endometrial regeneration, this project aim to elucidate the role of telomeres and telomerase associated proteins and their regulation in normal endometrial regeneration as well as their role in endometrial pathologies.

The student is expected to work with a team of researchers in University of Liverpool and Newcastle using a wide range of techniques, such as qPCR, western blotting, cellular imaging, immunohistochemistry, as well as advance bioinformatics tools and human tissue.

*Supervisor: D Hapangama*

*Contact email: dharani@liv.ac.uk*

c. **An exploratory Study aiming to explain why women menstruate?**  
(Hapangama)

Menstruation is the hallmark of “the reproductive period” in a woman’s life. However, it is not essential for conception and except for humans and upper order primates, most animals do not menstruate. The exact reason for menstrual shedding, which is a biologically expensive process is not understood. Some recent work has identified the accumulation of leucocytes and changes in the
cellular fate of the endometrium in the secretory phase of the endometrial cycle may hold the key to the reason why menstruation is necessary for the human endometrium.

This project explores this novel hypothesis by examining the dynamic changes in endometrial cell fate, using primary cell culture and explants tissue culture methods as well as advanced molecular biological techniques. The published and in house generated microarray data sets will also be interrogated using system biological tools. The student will have the opportunity to work with several groups collaborating with us to expand his/her data and to examine the aberrations in this process in conditions such as heavy menstrual bleeding. The data generated may present new treatment methods for common gynaecological disease.

**Supervisor: D Hapangama**

**Contact email:** dharani@liv.ac.uk

d. **Examination of the epithelial stem cell marker Lgr5 in endometriosis** (Hapangama)

Endometriosis is a common benign gynaecological condition with an unknown pathogenesis or curative treatment. Endometrial stem cells are postulated to play a central role in endometriosis yet no endometrial epithelial stem cell has been identified. LgR5 has been proposed as a universal epithelial stem cell marker in other tissues. Our recent work has confirmed the expression of LgR5 in the human endometrium using a variety of methods and we now propose to examine the differential expression of LgR5 and the LgR5 regulated genes in endometrial proliferative pathologies including endometriosis. The project will provide exposure to advanced molecular techniques such as in situ hybridisation, qPCR, laser capture micro-dissection and advanced bioinformatics.

**Supervisor: D Hapangama**

**Contact email:** dharani@liv.ac.uk

e. **Examination of NMR metabolomics to develop new, non-invasive diagnostic strategies in endometriosis and endometrial cancer** (Hapangama/Phelan)

Endometriosis is a common chronic inflammatory disease, defined by the existence of endometrial like stroma and epithelial tissue in ectopic sites, outside the uterine cavity. Although the prevalence of endometriosis is similar to common disease such as asthma, diagnosis requires an invasive surgery in the form of laparoscopy. Endometrial cancer on the other hand is the commonest gynaecological cancer with an alarmingly increasing incidence. New diagnostic and prognostic markers are expected to reduce the associated morbidity and mortality. This study aims to use NMR based metabolomics analysis, in the current diagnostic algorithm for endometriosis/endometrial cancer to improve diagnostic accuracy. The student will work with the clinical and research teams at the Liverpool Women’s Hospital, collecting biological material, as well as analysing the already collected biospecimens (serum) to identify variations in the concentrations of endogenous metabolites working with the team of researchers at the NMR Centre for Structural
Biology of the University of Liverpool. This project is expected to utilise advanced spectroscopy analysis of the material in parallel under the supervision of Prof Martin at the University of Lancaster.

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