Monash IVF Research and Education Foundation.

July 2020 to June 2021 Report.

Monash IVF Group


FREEZE CONTROL
CRYOBATH

Contents

A year in review

Comment from the Group CEO (on behalf of the Board)

Monash IVF Group Chief Executive Officer Michael Knaap

Monash IVF Group is committed to pioneering research and innovation to ensure that patient outcomes are continually improving.

Monash IVF Group Research and Education Foundation (MREF) in conjunction with the Group Scientific Advisory Committee (GSAC) have continued to drive research and innovation in FY21. Through a highly experienced scientific workforce engaged in research to advance our knowledge to continually optimise treatment outcomes, FY21 has seen expansion of our research and innovation portfolio which has advanced considerably.

Our footprint of IVF clinics, ultrasound practices and service centres across Australia and South East Asia includes over 700 dedicated doctors, scientific, nursing, allied health and support staff, complimented with many medical and scientific global leading researchers.

Monash IVF Group are committed to scientific leadership and clinical research and will continue to strive to break new ground through world class research and science as we aim to deliver above industry-based success rates, innovative services and attract partnership opportunities.

MREF provides an effective platform to ensure we continue to lead the world on the clinical and scientific front, building on our pioneering heritage, since achieving the world's first IVF pregnancy.

In 2021, the Group successfully submitted over 48 scientific papers and presentations both locally and internationally.

On behalf of the Monash IVF Group Board, I commend the MREF and relay my thanks to our doctors, scientists, staff and collaborators who have contributed to this strategically important body of work.

Excellence in Research and Education

Monash IVF Research and Education Foundation (MREF)

A word from the Chairman of the Monash IVF Research and Education Foundation Professor Robert McLachlan

Over the past decade as Chairman of MREF, I have been privileged to work with dedicated colleagues on my Advisory Board who provide first class clinical, embryological and medical imaging expertise. All members have worked with enthusiasm and diligence to address MREF strategic goals in original research and in scientific and clinical education. This work has continued despite the challenges presented by the COVID-19 pandemic and throughout this year, we have been heartened by the unwavering support of the Monash IVF Group Chief Executive Officer and the Board of Directors.

The Monash IVF Group's commitment to research and education has again been evident across 2020-2021, as it maintains its leadership position in assisted reproductive treatment. Our University collaborations now include Hudson Institute of Medical Research, RMIT, Monash, Melbourne, Adelaide and Newcastle Universities along with the Murdoch Children's Research Institute, all of which serve to diversify and enhance our research and teaching.

The MVF Group output July 1st 2020- June 30th 2021, and our future research directions, are outlined in this report. As always, I express my gratitude to my friend and colleagues on the Advisory Board, in particular, Professor Luk Rombauts, Director of Clinical Research, for his commitment and to our dedicated research team; Vivien MacLachlan, Data and Research Manager, and Samantha Ter, who diligently oversee the clinical studies and deal with the complex administrative demands, including human ethics committees' requirements. I would also like to thank all the Monash IVF Group clinical and scientific staff for their contributions to the educational programs.

In looking to the coming year, a review of MREF and the overall the research structure and governance at MVF Group will be undertaken to address the evolving strategic needs in this key area of its activities.

Monash IVF Research and Education Foundation Advisory Board

Professor Robert McLachlan

MBBS (Hons), PhD, FRACP, AM

Chairman MREF, Director of Clinical Research, Hudson Institute of Medical Research; Adjunct Professor, Monash Department of Obstetrics and Gynaecology; Medical Director, Healthy Male; Monash IVF Consultant Andrologist

Graduating from Monash University in 1977 and completing advanced training in endocrinology in 1984, Professor Rob McLachlan undertook his PhD studies in reproductive physiology at Prince Henry's Institute and the Department of Anatomy, Monash University. He worked as a visiting scientist at the University of Washington, in Seattle, USA, studying the hormonal regulation of reproductive function. After returning to Australia in 1990, he was a Research Fellow of the NHMRC until 2016 and continues to hold research grants. He has been the Consultant Andrologist to the Monash IVF program since 1991.

He is an Adjunct Professor in the Department of Obstetrics and Gynaecology at Monash University. As Director of Clinical Research at the Hudson Institute at Monash Medical Centre, his research contributions have involved basic and clinical research into male fertility regulation and the role of androgens. He has been Medical Director of Healthy Male [formerly Andrology Australia], a Federal government initiative, since 2006, and is committed to research and community and professional education in male reproductive health.

Since 2010, he has made over 81 invited presentations including 23 international meeting presentations (keynotes & plenaries). He has published around 300 original reports, reviews and chapters. He is Section Editor "Male Endocrinology" for www.ENDOTEXT.org. He is a Past President of the Fertility Society of Australia. In 2014 he received the Hoffenberg International Medal, Society for Endocrinology, UK, for outstanding contributions to the field. In 2016 was made a Member (AM) in the General Division of the Order of Australia in recognition of his work in male reproductive health and research. He was awarded Honorary Life Membership of both the Fertility Society of Australia and New Zealand (2019) and the Endocrine Society of Australia (2020).

Professor Luk Rombauts

PhD, MD, FRANZCOG, CREI

Research Director, MREF, Group Medical Director, Monash IVF; President of the Fertility Society of Australia and New Zealand, President of the World Endometriosis Society, Clinical Adjunct Professor, Department of Obstetrics and Gynaecology, Monash University; Head of Reproductive Medicine, Monash Health; IVF Specialist, Monash IVF Victoria

Trained in obstetrics and gynaecology at the University of Leuven, Belgium, in 1994, Professor Rombauts began his clinical and research work at Monash in 1994. After spending a further two years in the IVF unit at the Leuven Institute of Fertility and Embryology (Belgium), Professor Rombauts returned to Melbourne in 1998 to obtain his Certificate of Reproductive Endocrinology and Infertility (CREI). He is now accredited by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists as a training supervisor and examiner for the CREI.

Professor Rombauts has a strong track record in women's health, clinical and translational research in the field of reproductive medicine. He currently conducts NHMRC funded research into several aspects of female infertility, with a strong focus on the communication between the embryo and the endometrium. Professor Luk Rombauts has published more than 156 articles, reviews and book chapters since 1990. He has a current h-index of 37 (Scopus 2020) and a total of 4945 citations. He has been invited to present lectures at numerous international meetings. He has helped develop clinical guidelines for the management of PCOS, endometriosis and OHSS. He is also an expert advisor for the Endometriosis Phenome and Biobanking Harmonisation Project sponsored by the World Endometriosis Research Foundation.

He is an Adjunct Clinical Professor in the Department of Obstetrics and Gynaecology at Monash University and the Head of Reproductive Medicine at Monash Health. He is the Group Medical Director and Clinical Research Director of Monash IVF and a Research Fellow of the Hudson Institute for Medical Research. Professor Rombauts was elected as President of the Fertility Society of Australia in 2019. He is also the current President of the World Endometriosis Society and in 2011 he was appointed to the World Endometriosis Research Foundation Board of Trustees. He is also a member of the Endometriosis Australia Advisory Board and the Taiwanese Endometriosis Society's International Advisory Panel.

His clinical interests are advanced laparoscopic surgery for endometriosis, male and female reproductive microsurgery, and the management of male and female infertility, including all aspects of IVF.

Professor Beverley Vollenhoven

MBBS (Hons), PhD, FRANZCOG, CREI

Director Teaching and Learning, MREF. Professor and Acting Head Department of Obstetrics and Gynaecology, Monash University; Head of Gynaecology at Monash Health; IVF Specialist, Monash IVF Victoria

Professor Vollenhoven graduated from Monash University in 1984 and completed her training in Obstetrics and Gynaecology in 1995. Since 1996 she has been a clinician at Monash IVF and has a sub-specialty qualification in Reproductive Endocrinology and Infertility (CREI).

Her areas of clinical interest include infertility, polycystic ovarian syndrome, eating disorders, paediatric and adolescent gynaecology and menopause. She also has a clinical and research interest in the cause and treatment of uterine fibroids (leiomyomas); endometriosis; the management of infertility, particularly IVF ovulation and ovulation disorders (such as PCOS); Turner's Syndrome and menopause. She has more than 160 publications in both journals and books.

Professor Vollenhoven is the Head of Gynaecology at Monash Health, Victoria's busiest Gynaecology Service. She is the Acting Head of Obstetrics and Gynaecology at Monash University.

She is a Past Chairperson of the Victorian Regional Committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists. She is a member of the RANZCOG CREI committee and an examiner for the sub specialist exams. She was a member of the 8th Council of RANZCOG. She is a member of the Advisory Committee on Medicines for the TGA. She is currently on the board for the Fertility Society of Australia. In 2019 she became a member of the Victorian Honour Roll of Women. In 2021 she was awarded a Member (AM) in the General Division of the Order of Australia Queen's Birthday Honours. Professor Vollenhoven was appointed Director of Teaching and Learning, MREF in June 2012.

Associate Professor Deirdre Zander-Fox

BSc (Hons), PhD

Regional Scientific Director of Monash IVF Victoria and Malaysia, Associate Professor Monash University, University of South Australia and University of Adelaide

Deirdre completed her PhD studies in 2010 through The University of Adelaide's School of Paediatrics and Reproductive Health in which she undertook novel research into the impact of in vitro stress on preimplantation embryo development, viability and metabolism. She has been a clinical embryologist since 2004 and is currently the Monash IVF Group Regional Scientific Director and oversees Monash IVF Victoria and Malaysia and is responsible for Embryology, Genetics, Andrology and Endocrine services within these clinics as well as being chair of the Monash IVF Group Scientific Advisory Committee (GSAC) . In addition, Deirdre supervises numerous PhD and honours students and holds Adjunct Associate Professor positions at three major Australian Universities (Monash University, University of Adelaide and University of South Australia), as well as NHMRC funding.

Deirdre has authored over 40 peer reviewed journal articles and book chapters with her research primarily focusing on improving laboratory technology that will directly benefit infertile patients including cryopreservation, microinjection technology and culture media design. Her basic research interests focus on the impact of the environment during peri and pre-implantation development on programming fetal growth and offspring health.

Associate Professor Mark Green

BSc (Hons), PhD, FSRB

Deputy Scientific Director of Research at Monash IVF Victoria, Associate Professor, Group Leader and Director of Teaching & Learning, School of BioSciences, University of Melbourne

Mark completed his PhD at the University of Nottingham in the UK, before undertaking a two-year postdoctoral fellowship at the University of Missouri, USA. He then moved to New Zealand, to be the inaugural Maurice Paykel Fellow at The Liggins Institute, University of Auckland and subsequently, the inaugural Fertility Associates Fellow, working closely with New Zealand's largest human fertility clinic, to ascertain the effects of reproductive technologies on the phenotype and health of IVF children. During this time, Mark also held a joint appointment as a senior scientist studying the health of cloned animals with AgResearch Ltd. In 2011 Mark was recruited as the Merck Serono Lecturer in Reproductive Biology and group leader in the School of BioSciences, University of Melbourne. Alongside this in 2019, Mark started as the Deputy Scientific Director of Research at Monash IVF Victoria. In 2020, Mark was promoted to an Associate Professor and inducted as a Fellow of the Society for Reproductive Biology (SRB), due to his sustained research contributions, involvement and achievements in the area of reproductive biology.

Mark has published more than 50 journal articles and book chapters, with his research frequently featured in the media. He has founded two start-up companies to commercialise his patents in microfluidic sperm sorting technologies. Mark has received national research awards and sits on numerous committees and scientific boards in the reproductive biology discipline. He has successfully secured greater than $11 million in research funding and currently holds NHMRC and ARC research grants. His research focusses on understanding how environmental factors, such as endocrine disruptors, light pollution and heat stress, as well as assisted reproductive technologies, affect gamete quality, early embryo development and offspring health.

Associate Professor David Shaker

MBBCh FRCS, FRGOG, FRANZCOG, MMEd (Dundee)

Associate Professor, Department of Obstetrics and Gynaecology, University of Queensland; IVF Specialist, Monash IVF Queensland

Dr Shaker graduated in 1986 and attained Fellowship of the Royal College of Surgeons of Edinburgh, UK (FRCS) in 1993. Later, he attained membership of the Royal College of Obstetricians & Gynaecologists (RCOG) UK in 1995. He received special training in advanced laparoscopic surgery and obtained RCOG certificate of laparoscopic surgical training.

Dr Shaker worked in different consultant positions in UK before moving to Australia in 2007, to take a consultant position at Rockhampton Hospital. He was appointed as Associate Professor at the University of Queensland in 2013. He also is a member of the board of examiners of Royal Australasian College of Obstetricians and Gynaecologists (FRANZCOG) and the Australian Medical Council Exam (AMC).

Besides his clinical work, Dr Shaker has special interest in medical education and scholarship in medicine. He completed a Master's degree in medical education at the University of Dundee, UK. His thesis focused on the process of learning and teaching surgical techniques. He also is a member of the Faculty of Surgical Trainers, Royal College of Surgeons Edinburgh, UK and a member of the Editorial Board for the RCOG continuous professional development Journal (The Obstetrician and Gynaecologist).

Dr Shaker currently practices as a private obstetrician and gynaecologist at Rockhampton and IVF specialist at Monash IVF Rockhampton.

Associate Professor Yanhe Liu

BSc, MSc, MCE, PhD

Scientific Director Monash IVF Queensland; Honorary Adjunct Associate Professor, Bond University; Adjunct Senior Lecturer, University of Western Australia and Edith Cowan University

Yanhe has been a clinical embryologist since 2002, with extensive experience in IVF laboratory management both in Australia and overseas. He achieved his Master's degree in Clinical Embryology at Monash University in 2009, followed by a PhD through Edith Cowan University in 2016 while working part time. His PhD project has focused on time-lapse embryo selection, with seven resulting publications on the top fertility journals including Fertility and Sterility. Yanhe is currently the Scientific Director at Monash IVF QLD, overseeing the operation and scientific development of Embryology, Andrology and Biochemistry in all our Queensland laboratories.

Yanhe is an internationally recognised expert in embryo selection and has been frequently invited to speak at conferences and to participate in the peer review process with a number of top fertility journals (including Human Reproduction Update, Human Reproduction, and Journal of Assisted Reproduction and Genetics). He was awarded Top Reviewer by Human Reproduction in both 2016 and 2018. His research interests focus on the clinical introduction of novel techniques to improve IVF success rate. He has authored/coauthored more than 20 publications in the last seven years. Currently he is an associate editor for the journal Human Reproduction.

Professor Moira O'Bryan

PhD

Professor and Dean of the Faculty of Science, The University of Melbourne, Victoria.

The University of Melbourne has appointed Professor Moira O'Bryan as Dean of the Faculty of Science.

Professor O'Bryan has been Head of the School of Biological Sciences within the Faculty of Science at Monash University for three and a half years.

Prior to this role, she was the Deputy Director of Monash Biomedicine Discovery Institute, and Program Lead for the 'Development and Stem Cells program' within the Faculty of Medicine, Nursing and Health Sciences, also at Monash.

Professor O'Bryan is a developmental biologist and reproductive biologist, and a noted national and international researcher on male reproductive health. She is the current President of the Society for Reproductive Biology (Australia and New Zealand).

Monash IVF Victoria and Queensland, ongoing projects

Piezo ICSI: Can an alternative type of intracytoplasmic sperm injection (ICSI) for eggs improve fertilisation

Prof Luk Rombauts[1], Kate Watson[2], A/Prof Hassan Bakos[3], A/Prof Deirdre Zander-Fox[1]

[1]Monash IVF Group, Clayton; [2]Monash IVF, Queensland, [3] Monash IVF NSW

The standard method for ICSI was developed in the 1990's and involves using a sharp needle to pierce the zona pellucida and the cell membrane in order to place the sperm inside the egg. In addition, it is necessary to aspirate the cytoplasm of the oocyte up into the pipette and then to expel back into the egg, to ensure that the membrane is pierced. This procedure revolutionised the treatment for male infertility. The fertilization rates for this method across the group range between 65-70% and approximately 8-12% of eggs do not survive this piercing method and lyse.

Piezo ICSI which has been used for many years for animal IVF has recently been used in Japan. This method involves ultrasonic movement of a pipette that gently bores its way through first the zona pellucida and then the cell membrane. This method uses a blunt pipette and does not require the cytoplasm to be aspirated. As a result it has been reported that this method enables more gently placement of the sperm in the oocyte and reduces the lysis rate of eggs, overall increasing fertilization rates.

This study is to assess the effect of Piezo ICSI on fertilization rates and degeneration rates in a sibling split study across 5 Monash IVF group sites within Australia.

Felix- Method for Separating DNA intact sperm to improve IVF Outcomes

A/Prof Hassan Bakos[1], A/Prof Deidre Zander-Fox[1] and Prof Rob McLachlan[1], Prof John Aitken[3]

[1]Monash IVF NSW; [2]Monash IVF Victoria; [3]Hunter Medical Research Institute, NSW

Current semen preparation methods in ART do not assess the impact on all sperm molecular aspects that may impact fertilization. Methods for the selection of sperm for ICSI are usually based on low magnification selection of the morphology of a motile sperm. These parameters do not provide any assessment of the molecular health of the sperm. Sperm with high levels of DNA damage are known to result in reduce fertilization rates, poorer embryo development, reduced pregnancy rates and increased levels of miscarriage.

The Felix medical device uses electrophoresis to separate DNA intact sperm. This study will assess the ability of the Felix device to separate DNA intact sperm and to improve IVF outcomes. The initial aim of this study is to assess the impact of Felix method compared with existing sperm selection methodologies. The second aim is to engage in a clinical trial sibling split design which will be used to determine the effect of Felix sperm separation on fertilization rates and embryo development. Secondary outcomes will include DNA damage levels in sperm and pregnancy rates. This study is being conducted in collaboration with Memphasys Ltd as the commercial partner producing the Felix sperm separation device.

Establishment and validation of the 'exposome' as a prognostic predictor of female fertility

A/Prof Mark Green[1,2], Dr Bradley Clarke[3], A/Prof Deidre Zander-Fox[1], Prof Luk Rombauts[1]

[1]Monash IVF, Clayton; [2]School of BioSciences University of Melbourne, Parkville; [3]School of Chemistry University of Melbourne, Parkville

There is now an increasing reliance on ART in order to reproduce. It is postulated that rising infertility can be partially attributed to exposure to man-made environmental toxicants, such as endocrine disrupting chemicals (EDCs). The aims of this project are 1) to establish and validate methodologies to quantify the 'exposome', specifically paraben, phthalate and per-/poly-fluoroalkyl substances (PFAS) concentrations in human urine and follicular fluid samples (n=150 patients), and 2) to provide preliminary data to determine whether the exposome can be used as a reliable prognostic marker for egg quality and thus fertility. This research will establish a brand-new academic collaboration. The project outcomes have substantial scope for direct uptake and future investment by Monash IVF, as a clinical test to be offered to patients.

Which factors are associated with repeated implantation failure in couples undergoing IVF/ICSI?

Dr Fabrizzio Horta[1,3], Prof Beverley Vollenhoven[2,3], Prof Ben W Mol[2], Dr Sarah Hunt[2,3], A/Prof Mark Green[3], A/Prof Deirdre Zander Fox[3], A/Prof Peter Temple-Smith[1], Dr Sally Catt[1]

[1]EPRD Monash University, Clayton; [2]Monash Dept Obstetrics and Gynaecology, Clayton; [3]Monash IVF, Clayton

Recurrent implantation failure (RIF) refers to the non-occurrence of pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles. RIF can be the consequence of male contribution/sperm, embryonic or uterine factors including disrupted endometrial receptivity. Sperm DNA damage, thrombophilia and immunological issues as well as factors affecting endometrial receptivity, have been suggested as important to consider in couples with RIF. While many infertile couples with RIF currently are undergoing such testing and subsequent treatment, the scientific knowledge underpinning these tests is lacking. The aim of this study is to assess whether the presence of hereditary and acquired thrombophilia and / or sperm DNA damage are related to RIF in couples with idiopathic infertility. We propose a case-control study with 80 couples (two groups; 40 couples/group). Cases will be couples with RIF, defined as above.

Controls will be age-matched couples scheduled for their first IVF cycle. Women with previous ovarian hyperstimulation syndrome, poor responders and women with ≥20 cumulus oocytes complexes retrieved at OPU will be excluded. We propose a novel approach not requiring randomization. Couples in the cases and control group will undergo testing for inherited and acquired thrombophilia and sperm DNA damage. Chi-square, logistic regression and ROC-analysis will be used to compare the results. In the absence of an association, thrombophilia or sperm DNA damage can be excluded from a role in RIF.

Oocyte DNA repair capacity as a novel marker for female ageing in IVF/ICSI cycles

Dr Fabrizzio Horta[1,3], Prof Beverley Vollenhoven[2,3], A/Prof Peter Temple-Smith[1], Dr Sally Catt[1], A/Prof Mark Green[3], A/Prof Deirdre Zander-Fox[3]

[1]EPRD Monash University, Clayton; [2]Monash Dept Obstetrics and Gynaecology, Clayton; [3]Monash IVF, Clayton

Reproductive outcomes for women undergoing ART declines with age. Ageing and oocyte quality have been associated with aneuploidy, however, the factors determining oocyte quality remain unclear. Critical markers of DNA damage response (DDR) have been shown to decrease in the mouse model regardless of the oocyte stage during aging. Furthermore, a diminished DNA repair capacity and negative effects on embryo development have been found in the presence of DNA insults in gametes. This emerging data requires exploratory studies in humans to examine potential novel oocyte quality markers linked to IVF/ICSI clinical outcomes and male/sperm contribution. To examine the potential effect of female age on the DNA repair capacity makers of human oocytes on IVF/ICSI clinical outcomes, we propose a prospective cohort study including women presenting with either primary or secondary idiopathic infertility. Couples will be allocated into three groups according to female age: <30, 30-39 and ≥40 years old. Immature oocytes will be assessed for NADH, ATM and ãH2AX levels and leftover sperm samples used for IVF/ICSI cycles will undergo DNA damage testing. Women with known uterine pathologies, endometriosis, polycystic ovarian syndrome, ovarian hyperstimulation syndrome and poor responders will be excluded. Sample size; 60 couples, 20 couples per study group.

We propose shared research costs with Monash University. DDR makers will be assessed simultaneously in each oocyte collected. Markers will be analysed using ANOVA and clinical outcomes through Chi-square and logistic-regression analysis. Gamete studies will be conducted at Monash University aiming to develop two publications.

Post-thaw viability and function of ovarian tissue cryopreserved by slow-freezing or vitrification

Dr Sally Catt[1], A/Prof Deirdre Zander-Fox[2], A/Prof Peter Temple-Smith[1], Dr Fabrizzio Horta[1,2], Dr Kiri Beilby[1], Prof Beverley Vollenhoven[2,3]

[1]EPRD Monash University, Clayton; [2]Monash IVF, Clayton; [3]Monash Dept Obstetrics and Gynaecology, Clayton

While ovarian tissue has been collected and stored from many patients (predominantly cancer patients) over the years, there is little indication as to whether this tissue will survive the freeze-thaw process, or if the tissue has the right complement of follicles to be useful if transferred as an ovarian graft. Pregnancies from *in vivo* transplantation are very rare around the world, and to date, no pregnancies have arisen from oocytes resulting from *in vitro* follicle growth, although it has been demonstrated in mice (Wang et al, 2009 and 2011).

The aims of this study are: i) to thaw frozen ovarian tissue, consented for research, from a range of patient ages and analyse follicular dynamics and viability, using histology, immunofluorescence and follicular isolation (*in vitro* growth), and ii) to compare traditional slow cooling ovarian tissue freezing methods with vitrification using similar *in vivo* and *in vitro* techniques, and oocyte maturation as an end point.

In the future, it could be routine for patients to have 10% of the tissue analysed soon after cryopreservation (with the best freeze technique in place). This would give a guide to patients and the clinic as to what they have frozen and how 'useful' it could be for future fertility. It is anticipated that either a Monash IVF embryologist, enrolled as a masters student, and given enough time to complete this study with supervision and training from all investigators but principally EPRD staff, or a suitable student, chosen from outside Monash IVF, will undertake the study. Sheep ovaries will be used as a model for training and evaluation.

Genetic studies on male infertility and the trans-generational health of children conceived through ART

Prof Moira O'Bryan[1], Dr Sarah Catford[2], Prof Robert McLachlan[2,3], Dr Gideon Blecher, Dr Ie-Wen Sim[3], Dr Darren Katz[4], Prof Luk Rombauts[3]

[1]Dept. Anatomy and Developmental Biology, Monash University; [2]Hudson Institute of Medical Research, Clayton; [3]Monash IVF, Clayton; [4]Men's Health Melbourne

Infertility affects 1 in 20 Australian men and male factors are involved in about half of all ART treatments. Most often there is an unexplained failure of the testicular sperm tubules to produce adequate numbers of motile sperm capable of fertilisation. Genetic factors are suspected to be causal in many cases. Understanding such genetic factors may result in new diagnostic tests and ultimately specific treatments. Such research may also address uncertainties around the possible transmission of infertility to ART-conceived offspring.

With improved genetic analytical techniques and bioinformatics, we are increasingly finding genetic variants that are the likely/certain to be the cause of the man's infertility or maybe risk factors without certainty that they are the primary or even contributory cause. Indeed, some detected changes may well not be biologically significant variants.

This complex study continues to use samples from the Monash Male infertility data set, and in collaboration with the leading overseas investigators, as a part of the International Male Infertility Genetics Consortium (www.imigc.org), will forge ahead until we can resolve the extent and impact of genetic variants in male factor infertility, including for the general and reproductive health of the man and his offspring.

Podocalyxin identified as a key negative regulator of human endometrial epithelial receptivity

Prof Guiying Nie[1], Prof Luk Rombauts[2,3]

[1]RMIT University, Bundoora; [2]Monash IVF, Clayton; [3]Monash Dept Obstetrics and Gynaecology, Clayton

ART has progressed into an important medical intervention to overcome infertility. However, despite significant advancements in embryo culture, selection and transfer techniques, implantation failure still poses a crucial limiting factor. It is believed that the problem is the "soil for the seeds", the endometrium. For implantation to occur, the endometrium must differentiate into a receptive state. As the embryo first contacts the surface of the endometrial epithelium, this surface must become adhesive for embryo attachment. Although it is known that the endometrial epithelium remodels structurally and functionally to gain receptivity, the exact molecular changes are not well understood. A widely held view is that up-regulation of adhesion-promoting molecules is important, but the details are not well characterized. Our studies discovered a concept contrasting to the commonly held notion of receptivity establishment – the endometrium needs to remove a key negative regulator. This regulator is a membrane protein called podocalyxin, which is expressed in all endometrial epithelial cells and inhibits embryo implantation. During the establishment of receptivity, podocalyxin is down-regulated in the luminal epithelial cells, selectively converting the endometrial surface from a non-receptive to an implantation-permitting state. Our studies further suggest that epithelial podocalyxin may provide a new parameter for optimizing and evaluating endometrial receptivity.

Health and fertility in ICSI-conceived young adult males of severely infertile fathers

Prof Jane Halliday [1], Dr Sharon Lewis [1], Dr Sarah Catford[2], Prof Moira O'Bryan[3], Prof Robert McLachlan[2,4].

[1] Murdoch Childrens Research Institute, Parkville; [2]Hudson Institute of Medical Research, Clayton; [3]Monash University, [4]Monash IVF, Clayton

Infertility is common, affecting 15% of couples and ~65,000 Assisted Reproductive Technology (ART) cycles are undertaken each year in Australia. About one third of cycles are for male factor infertility. In many, the reason for reduced sperm number or quality is spermatogenic failure (STF) of unknown cause. Intra-cytoplasmic sperm injection (ICSI) is the commonest ART method. ICSI-conceived offspring of severely infertile men have higher rates of congenital anomalies, which may be due to patient factors and/or the ICSI technique. However, little is known about the health of ICSI-conceived adults, and in particular, the health and reproductive potential of ICSI-conceived men. Only one small study to date has assessed semen parameters and reproductive hormones in ICSI-conceived men and suggested higher rates of impaired semen quality compared to spontaneously conceived (SC) peers while metabolic data was similar.

This cohort study aims to evaluate the general health and development, fertility and metabolic parameters and, epigenetic signatures of ICSI-conceived sons whose fathers had poor semen quality due to spermatogenic failure compared to three age-matched control groups, [1] ICSI-conceived sons whose fathers with obstructive azoospermia (OAZ), [2] IVF-conceived sons and [3] spontaneously conceived sons, recruited from other studies.

Of 1112 ICSI parents including fathers with STF and OAZ, 78% (n=867) of mothers and 74% (n=823) of fathers were traced and contacted. ICSI sons were recruited from March 2017 to July 2020. Based on preliminary participation rates, we estimate the following sample size will be achieved for the ICSI study group: mothers n=275, fathers n=225, sons n=115. Outcome measures include validated survey questions, physical examination, reproductive hormones, serum metabolic parameters and semen analysis. For epigenetic and future genetic analyses, ICSI sons provide specimens of blood, saliva, sperm and seminal fluid while their parents provide a saliva sample.

The primary outcomes of interest are the number of mother-reported hospitalisations of the son; son-reported quality of life; prevalence of moderate-severe oligozoospermia (sperm concentration <5 million/ml); and DNA methylation profile. Data analysis is currently underway. The new knowledge generated from these results will direct research into treatment safety and patient counselling.

CSF3 Receptor blockade to restore endometrial receptivity in idiopathic infertile women

Dr Tracey Edgell[1], Prof Luk Rombauts[2], Prof Beverley Vollenhoven[2]

[1]Hudson Institute of Medical Research, Clayton; [2]Monash IVF, Clayton

Despite improved embryo technologies, IVF fails to fulfil its promise for many women. Women often undergo multiple cycles without achieving a pregnancy. Increasingly it is recognised that the maternal endometrium is a critical component in achieving pregnancy success. Our published studies have identified that CSF3 to significantly elevated within the uterine cavity of idiopathic infertile women (Edgell et al, Cytokine. 2018; 111:222-229). In these infertile women the CSF3 receptor (CSF3R) is found reduced or absent from the endometrial tissue. Functional studies have demonstrated that CSF3 significantly impacts both endometrial cell and trophoblast cell behaviours. Together the data demonstrates the importance of the CSF3 axis during the early stages of embryo attachment and invasion.

This study examined the potential to target the excess CSF3 concentrations to improve endometrial receptivity using specific antibodies to blockade the receptor, preventing its reduction/loss from the endometrial surface. Utilising antibodies directed to the CSF3 receptor, we examined CSF3R expression on endometrial cells following exposure to elevated concentrations of CSF3. It was observed that the molecular mass of CSF3 receptor protein evident on endometrial cells differed to the multiple forms that are widely characterised in immune cells. Studies of proliferation and adhesion of endometrial and trophoblast cells elicited a small but not statistically significant change in cell behaviours. Outcomes of the study were potentially impacted by poor antibody recognition of the novel endometrial form of CSF3R.

Australian Male Infertility Exposure study (AMIE)

Prof Jane Halliday[1], Dr Sarah Briggs[1], Prof Robert McLachlan[1,2] and Prof Luk Rombauts[2]

[1]Reproductive Epidemiology, Murdoch Children's Research Institute; [2]Monash IVF Group, Richmond

The aim of the AMIE study is to develop a better understanding of the impact of lifestyle and environment on male infertility. Tens of thousands of couples trying to have children in Australia have fertility issues. Almost half of these are due to problems concerning the man. Unfortunately, not much is known about the causes of male infertility. There is some research that suggests lifestyle or environmental factors could play a part. We know that smoking, diet or environmental pollutants can lead to diseases like cancer or diabetes. What we do not know is whether these are also related to infertility.

The AMIE study seeks to understand how health, lifestyle and environmental factors may impact on male infertility and treatment outcomes for male infertility. This study is being done by an expert team of scientists and clinicians, led by the Reproductive Epidemiology group at the Murdoch Children's Research Institute (MCRI). It involves participation from many fertility clinics all around Australia, including Monash IVF.

Contributions to Scientific Literature

The following compiles a portfolio of contributions to the scientific literature by Monash IVF doctors, staff and key collaborators for July 2020 to June 2021. The list represents our commitment to broad range of research interests spanning reproductive biology, genetic and molecular, andrology, clinical and psychological based research.

Peer Reviewed Journal Articles/Publications

1. Al-Zubaidi U, Adhikari D, Cinar O, Zhang QH, Yuen WS, Murphy MP, Rombauts L, Robker RL, Carroll J. Mitochondria-targeted therapeutics, MitoQ and BGP-15, reverse aging-associated meiotic spindle defects in mouse and human oocyte. Hum Reprod. 2021 Feb; 36(3): 771-784.
2. Brits C, Feenan K, Chapple V, Matson PL, Liu YH. Time-lapse videography reveals different morphokinetic profiles of human embryos displaying direct or reverse cleavage at different stages of development: A retrospective sibling embryo study. Asian Pac J Reprod. 2020 Nov; 9:261-266.
3. Catford S, Lewis S, Halliday J, Kennedy J, O'Bryan MK, McBain J, Amor DJ, Rombauts L, Saffery R, Hart RJ, McLachlan RI. Health and fertility of ICSI-conceived young men: study protocol. Human Reprod Open. 2020 Oct; 2020(4): 1-12.
4. Filby CE, Rombauts L, Montgomery GW, Giudice LC, Gargett CE. Cellular Origins of Endometriosis: Towards novel diagnostics and therapeutics. Semin Reprod Med. 2020; 38: 1-15.
5. Higgins C, Fernandes H, Da Silva Costa F, Martins WP, Vollenhoven B, Healey M. The impact of adenomyosis on IVF outcomes: a prospective cohort study. Hum Reprod Open. 2021 Apr; 2021 (2): 1-10.
6. Horta F, Ravichandran A, Catt S, Vollenhoven B, Temple-Smith P. Ageing and ovarian stimulation modulate the relative levels of transcript abundance of oocyte DNA repair genes during the germinal vesicle-metaphase II transition in mice. J Assist Reprod Genet. 2021 Jan; 38(1):55-69.
7. Hunt S, Abdallah KS, Ng E, Rombauts L, Vollenhoven B, Mol BW. Impairment of Uterine contractility is associated with unexplained infertility. Semin Reprod Med. 2020 Oct; 38 (1): 61-73.
8. Hunt S, Low X, Dunn M, Da Silva Costa, Vollenhoven B, Mol BW, Rombauts L. Assessing Peristalsis at the endometrial-myometrial junctional zone: A reproducible ultrasound technique? Fert & Reprod. 2020 Oct; 2(3): 96-101.
9. Kemper JM, Liu Y, Afnan M, Hammond ER, Morbeck DE, Mol BWJ. Should we look for a low-grade threshold for blastocyst transfer? A scoping review. Reprod Biomed Online. 2021 Apr; 42(4): 709-716.
10. Nikitaras V, Zander-Fox D, McPherson NO. Improving sperm oxidative stress and embryo quality in advanced paternal age using Idebenone in vitro – A proof-of-concept study. Antioxidants. 2021 June; 10: 1-16.
11. Rai A, Poh QH, Fatmous M, Fang H, Gurung S, Vollenhoven B, Salamonsen LA, Greening DW. Proteomic profiling of human uterine extracellular vesicles reveals dynamic regulation of key players of embryo implantation and fertility during menstrual cycle. Proteomics. 2021 Feb; 21 (13-14).
12. Ratner RT, Tsaltas J, Vollenhoven B. Hysteroscopy and the risk of gas embolism: A review. JEPPD. 2020; 12(1): 51-55.
13. Watson K, Korman I, Liu Y, Zander-Fox D. Live birth in a complete zona-free patient: a case report. J Assist Reprod Genet. 2021 May; 38(5):1109-1113.

Presentations- National Conferences and Meetings

1. McLachlan R. Male fertility, the canary in the mine. SEED Meeting; 2021, May 22-23: Sydney, Australia.
2. Rombauts L. Precision medicine applied to the gamete. SEED Meeting; 2021, May 22-23: Sydney, Australia.
3. Rombauts L. Manipulation: Are we doing the right thing? SEED Meeting; 2021, May 22-23: Sydney, Australia.
4. Rombauts L. Stump the Professor. RANZCOG Virtual Annual Scientific Meeting; 2021, February: Online.
5. Rombauts L. Endometriosis: the perspective of the surgeon. Endometriosis Ultrasound Credential ASUM; 2020, August 01: Online.
6. Zander-Fox D. NI-PGT: From research to clinical practice. Vitrolife Genomics Webinar Series; 2020, May: Online.
7. Zander-Fox D. PIEZO ICSI: Better or Not? ASPIRE Webinar series; 2020, Oct 16: Online.
8. Zander-Fox D. The future of non-PGT embryo selection. SEED Meeting; 2021, May 22-23: Sydney, Australia.
9. Zander-Fox D. Embryo selection: The Past, Present and Future. MSD/ Organon Nurses Meeting; 2021: Online.

Presentations- International Conferences and Meetings

1. Zander-Fox D. Efficacy of PIEZO ICSI to improve fertilization and decrease oocyte degeneration rates. ASPIRE; 2021, May 01: Online.
2. Rombauts L. Endometriosis: Surgery or IVF? The Israel Fertility Association; 2021, May 7: Online.
3. Rombauts L. How cognitive bias affect the surgeon. 14th World Congress of Endometriosis; 2021, March 6-10: Online.

Poster presentations and Abstracts- National Conferences and Meetings

1. Rogers-Kelso M, Watson K, Ong K, Shaker D, Korman I, Turner R, Liu Y. Six-hour short insemination leads to reduced fertilization but improved pregnancy outcomes. Scientists in Reproductive Technology (SIRT) Virtual conference, Australia; 2021 May 1-2; Online.
2. Williams A, Phung A, Popkiss S, Horta F, Green MP, Zander-Fox D. Efficacy of SpermSlow medium on fertilization, degeneration, utilization and pregnancy rates in male-factor infertility ICSI cycles. Scientists in Reproductive Technology (SIRT) Virtual conference Australia; 2021, May 1-2: Online.

Poster presentations and Abstracts- International Conferences and Meetings

1. Cutting E, Mol BW, Vollenhoven B, Catt S, Horta F. Effects of COVID-19 quarantine period on fertility treatment and IVF clinic management. ESHRE 37th Annual meeting; 2021 June 26- July 1; Online conference.
2. Liu Y, Ong K, Korman I, Turner R, Leyden M, Zander-Fox D, Rombauts L. Timing of blastocyst observation on day 5: effect on the assessment to predict live birth, and the incorporation into a blastocyst selection model. ESHRE 37th Annual meeting; 2021 June 26- July 1; Online conference.
3. Orevich LS, Watson K, Ong K, Korman I, Turner R, Liu Y. Time-lapse videography reveals morphometric and morphokinetic differences in the pronuclei of male and female human zygotes. ESHRE 37th Annual meeting; 2021 June 26- July 1; Online conference.
4. Ross T. To transfer or to discard: A retrospective analysis of ploidy, implantation and birthweight outcomes of grade "C" blastocysts following preimplantation genetic testing for aneuploidy (PGT-A). ESHRE 37th Annual meeting; 2021 June 26- July 1; Online conference.
5. Watson K, Ong K, Korman I, Turner R, Vollenhoven B, Zander-Fox D, Liu Y. Slow day 5 development affects implantation potential of fresh transferred embryos but not birthweight once pregnancy occurs: A multi-center retrospective cohort study. ESHRE 37th Annual meeting; 2021 June 26- July 1; Online conference.
6. Zander-Fox D. Efficacy of PIEZO ICSI to improve fertilization and decrease oocyte degeneration rates. ASPIRE 2021 Virtual Congress; 2021 April 30 – May 2; Online conference.

MREF external research grants attracted in July 2020 - June 2021

Professor Robert McLachlan

NHMRC Research Grants

2016-2021

NHMRC Project Grant #1120356, Associate Investigator (AI). "The genetic causes of male infertility".

Medical Research Future Fund [MRFF] Research Grant

2020-2023 MRFF Emerging Priorities and Consumer Driven Research initiative #EPCD000007, Chief investigator (CIB). "Men and Infertility over the Lifecourse (MAIL)'.

Professor Luk Rombauts

NHMRC Research grants

2019-2021 NHMRC Project Grant #1156666 (CIB). "The magic shield of the human uterus and fate of embryo implantation"

2019-2020 NHMRC Development Grant #1159714 (CIC). "Validation of a Prognostic Assay for Embryo Transfer"

2018-2021 NHMRC Project Grant #1139568 (CIC). "Human embryo's secret weapon for implantation"

2018-2020 NHMRC Development Grant #1136065. "Improving oocyte mitochondrial DNA copy number to enhance female reproductive capacity"

2017-2020 NHMRC Development Grant. Associate Investigator (AI). "Improving oocyte mitochondrial DNA copy number to enhance female reproductive capacity"

2017-2021 NHMRC Project Grant #1139568, Associate Investigator (AI). "Human embryo's secret weapon for implantation"

2016 – 2021 NHMRC Project Grant #1120689, Associate Investigator (AI). "Facilitating endometrial receptivity to improve pregnancy outcomes"

ESHRE Research grants

2017-2020 Chief Investigator (CIB). "Elucidating a new mechanism of endometrial receptivity establishment in women and its clinical significance"

Professor Beverly Vollenhoven

NHMRC Research grants

2020-2023 NHMRC New Ideas Grant #1185467 (CIB). "Pregnancy and childhood outcomes associated with novel medication use in early pregnancy following IVF-assisted conception"

2019-2020 NHMRC Development Grant. "Validation of a prognostic assay for embryo transfer outcome"

2018-2020 NHMRC Grant #1139489. "Reappraisal of the mechanisms underlying implantation success or failure"

2017-2020 NHMRC Project Grant #1139489, Associate Investigator (AI). "Reappraisal of the mechanisms underlying implantation success or failure"

Other Research grants

2021-2022 Fertility Society of Australia and New Zealand. "Improving embryo selection in IVF treatments through incorporating novel non-invasive live-cell metabolic imaging of embryos using adapted confocal microscopy: a live birth safety study".

Awards

2021 Stillbirth Foundation Australia. "The endometrial environment: A new target to understand and prevent preterm stillbirth"

A/Professor Deirdre Zander-Fox

NHMRC Research grants

2019-2023 NHMRC Development Grant #1171821 (CIC) Genome-Wide Non-Invasive Prenatal Testing based on Circulating Trophoblastic Fetal Cells.

2020-2024 NHMRC New Ideas Grant #143467 (CIC). "Mitigating the risks of mitochondrial disease".

A/Professor Mark Green

NHMRC Research grants

2019-2023 NHMRC Targeted Call for PFAS (CIB) "Utilising male fertility as a biomarker of health to understand the biological effects of PFAS".

Other Research grants

2019-2022 ARC Discovery grant (CIB) "The impact of environmental toxicants on fertility of female animals".

2021 E=mc2 Initiative Grant. "Establishment and validation of the 'exposome' as a diagnostic measure of fertility and health".

Awards

Inducted as a Fellow of the Society for Reproductive Biology.

Media / Press

1. Newspaper article - Green MP. "I knew fertility could be an issue, but no one ever told David to worry". Sydney Morning Herald; 2021, May 09. Link: https://www.smh.com.au/lifestyle/health-and-wellness/they-knew-fertility-could-be-an-issue-but-no-one-ever-told-david-to-worry-20210429-p57ncz.html .
2. Expert Opinion - Green MP. "Are women delaying pregnancy because of the pandemic?" Primer; 2021, Feb 15.

Repromed Scientific Advisory Committee (SAC)

Gillian Homan

RN, RM, MN, BEd

Fertility Nurse, Clinical Research Manager, Chairman SAC (Repromed, South Australia)

Gillian has extensive experience as a Fertility Nurse and Manager and has a master's degree in nursing. She has a particular interest in pre-conception health and has worked with many couples in making lifestyle changes to improve their chance of conceiving a healthy baby. Gillian has also researched and published in her areas of interest and currently assists with several studies at Repromed. She is also the chair of the Repromed SAC committee.

Professor Kelton Tremellen

MB BS(Hons) PhD FRANZCOG CREI

Reproductive Endocrinology and Infertility Subspecialist, Medical Director – South Australia

Kelton Tremellen is a specialist Gynaecologist who also holds a sub-specialty qualification in Reproductive Endocrinology and Infertility (CREI). He also completed a PhD in Reproductive Immunology at the University of Adelaide.

Professor Tremellen is a Medical Director at Repromed, Adelaide and Professor of Reproductive Medicine, Flinders University. He has an active research interest in the fields of oxidative stress as a cause of male infertility, immune mediated implantation failure, ovarian reserve and the effect of nutritional supplements on fertility.

Professor Tremellen was the first to introduce AMH as a test of ovarian reserve to Australia in 2004 and is also the inventor of the male fertility pill Menevit (http://www.elevit.com.au/product-range/menevit/) marketed in Australasia by Bayer Consumer Care.

Dr Leanne Pacella-Ince

BHSc (Hons), PhD

Scientific Director Repromed and Fertility Tasmania

Leanne joined Repromed in 2007 and is the Scientific Director of Repromed and Fertility Tasmania. A fully qualified Embryologist, prior to becoming the Deputy Scientific Director of Dulwich, Leanne was the Genetics Co-ordinator for Repromed.

Completing her PhD under the supervision of Professor Michelle Lane and Associate Professor Deirdre Zander-Fox in 2014 through the University of Adelaide's School of Paediatrics and Reproductive Health for which she was awarded the Dean's Commendation for Thesis excellence. Her PhD focused on the contribution of perturbed granulosa and cumulus cell metabolism and mitochondrial protein levels to the poor IVF outcomes seen in women undergoing IVF with either reduced ovarian reserve or advanced maternal age.

In 2016, Leanne was awarded the Scientist in Reproductive Technology Established Scientist Award. With published papers in peer reviewed journals, Leanne is also an honors supervisor through the Adelaide University's Department of Obstetrics and Gynecology as well as an Australian Institute of Medical Scientists Assessor for IVF Embryologists.

She is also heavily involved in the implementation of new technology designed to provide better outcomes. Leanne is passionate about patient care and improving success rates.

Carole Tilbrook

RN, RM, BNg, Cert in Fertility Nursing (ESHRE)

Senior Fertility Nurse Specialist – Repromed

Carole has extensive experience as a Fertility Nurse and Manager at Repromed. She was also the first non-european Fertility Nurse to gain ESHRE accreditation. Carole has assisted in research during her time at Repromed and enjoys this facet of her role.

Associate Professor Mark Nottle

SAC External independent representative

Principal Research Fellow, Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide.

The SAC would like to recognise the invaluable work of Dr Nicole McPherson who diligently oversees recruitment for the clinical studies and deals with the complex demands of the medical, nursing and scientific staff, and human ethics committees.


Monash IVF

July 2020 – June 2021 Research Projects

Ongoing research

Efficacy of PIEZO ICSI to improve fertilisation rates of oocytes

A/Prof Deirdre Zander-Fox[1], Kevin Lam[2], Dr Leanne Pacella-Ince[2], Cathy Tully[2], Dr Hamish Hamilton[1], Kenichiro Hiraoka[3], Nicole O McPherson[2], Prof Kelton Tremellen[2]

[1]Monash IVF Group, Richmond; [2]Repromed, Dulwich; [3]Kameda Medical Centre, Makuhari

The first pregnancies using intracytoplasmic sperm injection (ICSI) were reported in 1992. Since that time ICSI has transitioned from being used to treat severe male factor infertility to being used as a treatment of choice for many other reasons including failed IVF insemination, embryo genetic testing and low oocyte number. In addition, the usage of ICSI has increased significantly with some countries reporting that ICSI is used in 100% of ART cycles. Although ICSI is a revolutionary technology in the field of ART, it is still invasive in its nature and the method, which involves aspiration of the cytoplasm, can result in increased rates of oocyte degeneration after the microinjection process is complete. PIEZO-ICSI is a modified microinjection process that uses a piezoelectric actuator to move the capillary in an ultra-rapid fashion resulting in microdrilling of the zona. This form of microinjection has been used successfully in various animal models to improve survival post microinjection. In addition, limited reports out of Japan have demonstrated that a significantly higher survival rate post injection was seen for oocytes being injected with PIEZO-ICSI rather than conventional ICSI, fertilisation rates were higher, PIEZO-ICSI increased the quality of D3 embryos compared to conventional ICSI, and also resulted in increased pregnancy rates and live birth rates. Therefore, a clinical trial was undertaken to test the hypothesis that PIEZO-ICSI technology will increase fertilisation rates and decrease oocyte degeneration rates compared to conventional ICSI as well as improving embryo quality and pregnancy rates compared to a prospectively matched cohort.

Acrosome reacted sperm – an innovative way to improve ICSI technology

Dr Nicole McPherson[1,2,3], Dr Hamish Hamilton[1], Kevin Lam[1], Marg Szemis[1].

[1]Repromed, Dulwich; [2]School of Medicine, University of Adelaide, Adelaide; [3]Freemasons Centre for Men's Health, University of Adelaide, Adelaide.

Before sperm has the capacity to fertilise and conceive a healthy embryo and fetus, it must first undergo post ejaculation maturation (capacitation, hyperactivation and acrosome reaction) which is initiated in the oviduct and by the cumulus oocyte complex. However, the current protocol for ICSI completely ignores this post ejaculation sperm maturation, with direct injection of sperm into the oocyte irrespective if their acrosomal status. This means that the oocytes receive a number of proteins and sperm plasma membrane components that they would not 'normally' receive. In rodent models it has been shown that injection of sperm which had not undergone this post ejaculation maturation (to mimic what is currently injected during ICSI) resulted in slower embryo cleavage and reduced pregnancy rates compared with embryos produced from natural mating. In addition, the human injection of acrosome reacted sperm resulted in a 4-fold increase in morula implantation rates compared with non-acrosome reacted sperm. These data suggest that while the oocyte has some capacity to deal with the incorporation of these 'extra' sperm molecules ,their addition is clearly having lasting effects to the developing embryo. Therefore, we hypotheses that inducing post ejaculation sperm maturation and the acrosome reaction in vitro prior to ICSI will increase blastocyst formation, implantation rates and live births.

Audit of the safety and efficacy of Intralipid therapy in early pregnancy

Richard Henshaw[1], Prof Kelton Tremellen[1]

[1]Repromed, Dulwich

The objective of this audit is to analyse maternal and fetal outcomes (side effects, pregnancy outcomes, pregnancy complications and congenital abnormalities) in women treated with Intralipid immunotherapy at Repromed since its introduction (2015).

Defining the male contribution to pregnancy immune tolerance deficit in women

Dr David Sharkey[2], Prof Sarah Robertson[2], Prof Kelton Tremellen[1].

[1]Repromed Dulwich, [2]Robinson Institute, University of Adelaide

To have a pregnancy free of complications and give couples the best chance of having a healthy baby, it is necessary to first prepare the mother's immune system to accept the developing fetus. A key step in preparing the female's body is through exposure to the conceiving partner's semen. Male semen, which is made up of sperm and a fluid called seminal plasma, contains several proteins that have been shown in humans and numerous animal species to communicate with the female reproductive tract and prepare the female tract for pregnancy. In this research study, a dance of proteins likely to be important in preparing the female body for pregnancy in both sperm and seminal plasma samples will be measured. Blood samples will be collected from the female and male partners to see how well the female's white blood cells can accept / suppress those of her male partner, which is a key indicator of having a female immune system prepared for pregnancy.

Together, we hope the results of this study will allow us to see whether the amount of these important proteins in semen and the function of white blood cells in women can be predictive of clinical pregnancy rate and likelihood of developing complications during pregnancy.

Male BMI as an indicator of IVF offspring gender

Prof Kelton Tremellen[1,2], Brittany Collie[2] (Medical Student Flinders University)

[1]Repromed, Dulwich, [2]Flinders University

This study aims to determine the impact of paternal BMI on sex ratio of babies born from IVF & ICSI treatment. It is a retrospective audit of IVF outcomes (gender of baby) and paternal BMI using data in RIMS.

Preimplantation Genetic Testing Using Next Generation Sequencing

Dr Tristan Hardy[1,2], Dr. Jan Liebelt[1,3,4], Hayley Salvemini[1], Dr. Tod Fullston[1,2], A/ Prof Deirdre Zander-Fox[5], Dr. Leanne Pacella-Ince[1], Prof Kelton Tremellen[1,6], Sam Tilley[1]

[1]Repromed, Dulwich, [2]SA Pathology; [3]The University of Adelaide, Adelaide; [4]The Womens & Childrens Hospital; [5]Monash IVF Group; [6]Flinders University

The purpose of this study is to improve the accuracy of embryo genetic testing by using next generation sequencing technology. The specific aims of the study are: 1. to identify all informative markers around the gene of interest in couples presenting for embryo genetic testing using targeted sequencing; 2. to perform targeted sequencing of embryos to create a more accurate digital fingerprint than the current method of DNA fingerprinting of embryos.

Couples will be recruited as part of their treatment cycle at Repromed. Following recruitment for PGT and planning of the cycle and feasibility studies using the standard method of karyomapping, the patientswill undergo standard IVF, intracytoplasmic sperm injection (ICSI) and embryo biopsy with genetic testing (karyomapping) as per their usual treatment cycle. Following the completion of the cycle, investigators will access stored DNA from the feasibility studies used to design the embryo genetic test and leftover DNA from embryo biopsies. This DNA is routinely kept following the completion of embryo genetic testing and is only available after the initial genetic testing is conclusive. Deidentified DNA samples will be sent to a sequencing facility for sequencing of the region of interest in the reference samples and embryos (typically around 2 million DNA nucleotides upstream and downstream of the genetic mutation). Bioinformatic analysis of the sequencing data will be performed separately to the analysis of clinical results using standard karyomapping. Comparison between the standard results and the karyomapping results will be performed in a blinded manner.

Relationship between Ejaculatory Abstinence and IVF outcomes

Prof Kelton Tremellen[1,2], Navya Jain[2]

[1]Repromed, Dulwich. [2]Flinders University

The aim of this study is to correlate period of abstinence from ejaculation before providing a semen sample for IVF-ICSI use with pregnancy outcomes for couples undergoing a fresh embryo transfer, while controlling for relevant male and female covariant of success (male age, BMI,smoking status and use of antioxidants; female age, BMI, ovarian reserve status and aetiology of infertility). It is a retrospective audit examining an existing data base (IVF report to the NPSU at UNSW) and RIMS notes.

Outcomes for women who utilise electively frozen oocytes

Anna Dalton[1], Juliette Koch[1]

[1]Repromed, Dulwich

This study is a Retrospective audit of notes to determine the utilisation rate of previously frozen oocytes, and the outcomes for their fertilisation rates, embryo transfer rates, clinical pregnancy rates and live birth rates.

Mackenzie's Mission: The Australian Reproductive Carrier Screening Project

Jan Liebelt[1,2,3], Tristan Hardy[1], Hayley Salvemini[1]

[1]Repromed, Dulwich; [2] Womens & Childrens Hospital, [3] The University of Adelaide, Adelaide

Reproductive genetic carrier screening (RGCS) is available in Australia with variable access for couples. At present, it is a fee-for-service test. In 2018, the Australian Federal Government announced an initiative, Mackenzie's Mission (MM), a research study investigating genetic carrier screening in 10,000 couples across Australia.

MM aims to:

- Develop a RGCS program and assess feasibility and acceptability of the program
- Evaluate reasons for couples accepting or declining to have RGCS
- Evaluate the uptake of RGCS, frequency of increased-risk couples and their reproductive decisions
- Evaluate the implementation of RGCS
- Identify possible barriers and facilitators, from couples, healthcare providers (HCPs), and the MM research team, to inform future service delivery
- Evaluate the screening experience
- Measure outcomes in the following domains: psychosocial impacts, ethical issues and health economic implications

Primary outcomes will include measures of: uptake variables, predictors of uptake, cohort characteristics of those who accept and those who decline RGCS, frequency of increased risk couples, and their reproductive decisions.

Predictive accuracy of cell free DNA testing in the detection of clinically significant rare autosomal trisomies and sub microscopic chromosomal abnormalities

Yvette Raymond[1], Dr Daniel Rolnik[1], Dr Shavi Fernando[1], Dr. Leanne Pacel-la-Ince[2], Dr Tristan Hardy[2]

[1]Monash Ultrasound for Women, Sydney Ultrasound for Women; [2]Repromed, Dulwich

This study is a retrospective audit of women who received high risk results for either RATs or segmental CNV on genome wide NIPT. Collection sites will include Monash Ultrasound for Women and Sydney Ultrasound for Women. After collection, we will be assessing the positive predictive value with 95% CI of expanded NIPT for our cohort, conducting a descriptive analysis of women who received high risk NIPT results with normal US findings for any trends in perinatal outcomes, and assessing what proportion of these women underwent subsequent invasive diagnostic testing.

Contributions to Scientific Literature

Peer Reviewed Journal Articles/Publications

1. Anand-Ivell R, Tremellen K, Soyama H, Enki D, Ivell R. Male seminal parameters are not associated with Leydig cell functional capacity in men. Andrology. 2021 Mar.
2. Kirk EP, Ong R, Boggs K, Hardy T, Righetti S, Kamien B, Roscioli T, Amor DJ, Bakshi M, Chung CWT, Colley A, Jamieson RV, Liebelt J, Ma A, Pachter N, Rajagopalan S, Ravine A, Wilson M, Caruana J, Casella R, Davis M, Edwards S, Archibald A, McGaughran J, Newson AJ, Laing NH, Delatycki MB. Gene selection for the Australian Reproductive genetic carrier screening project ("Mackenzie's Mission"). Eur J Hum Genet. 2021 Jan; 29(1): 79-87.
3. McPherson NO, Vincent AD, Pacella-Ince L, Tremellen K. Comparison of in vitro fertilisation/ intracytoplasmic sperm injection on live birth rates in couples with non-male factor infertility and advanced maternal age. J Assist Reprod Genet. 2021 Mar; 38(3): 669-678.
4. McPherson N, Vincent AD, Zander-Fox D, Grieger JA. Birthweight associations with parental obesity: retrospective analysis of 1,778 singleton term births following assisted repoductive treatment. 2021 Apr.
5. Song Z, Li W, O'Leary S, Roberts B, Alvino H, Tremellen K, Gadalla MA, Wang R, Mol BW. Can the use of diagnostic and prognostic categorisation tailor the need for assisted reproductive technology in infertile couples? ANZJOG. 2021 Apr; 61(2): 297-303.
6. Tremellen K, Pearce K. Small intestinal bacterial overgrowth (SIBO) as a potential cause of impaired spermatogenesis. Gut. 2020 Nov; 69(11): 2058-2059.
7. Tremellen K, Woodman R, Hill A, Shehadeh H, Lane M, Zander-Fox D. Use of a male antioxidant nutraceutical is associated with superior live birth rates during IVF treatment. Asian J Androl. 2021; 23: 16-23.
8. Tremellen K, Vincent AD, Pacella-Ince L, McPherson NO. Comparison of in vitro fertilisation/ intracytoplasmic sperm injection on live birth rates in couples with non-male factor infertility and advanced maternal age: overlooked details-response from authors. J Assist Reprod Genet. 2021 Apr.

Presentations- International Conferences and Meetings

1. Pacella-Ince L, Zander-Fox D, Goldsworthy C, Lane M. The effect of embryo biopsy on embryo health, development and viability. ASPIRE 2021 Virtual Congress; 2021 April 30 – May 2; Online conference.

New South Wales Research

Associate Professor Hassan Bakos

B. Hlth Sci (Hons), PH.D.(Med), Grad Cert. Mgt, CPMgr

Scientific Director, Monash IVF NSW & ACT; Conjoint Associate Professor, University of Newcastle

Associate Professor Hassan Bakos completed a Bachelor of Health Sciences and Honours Degree in Obstetrics and Gynaecology, University of Adelaide. In 2010, he completed a PhD in Reproductive Medicine for which he was awarded a special commendation from the Dean of Graduate Studies and the Robert Seamark award for the most outstanding graduating postgraduate candidature.

In 2011, Hassan was appointed as Deputy Scientific Director at Repromed where he supervised of the Andrology and Pathology services as well as performing clinical embryology procedures including ICSI and embryo biopsy. In 2015, he was appointed as Scientific Director for the Monash IVF Group in Sydney and is currently responsible for the scientific directorship and operations of six MVF laboratories across New South Wales and the Australian Capital Territory, including embryology, andrology and endocrinology services.

A/Prof. Bakos has held adjunct academic positions at the University of Adelaide and University of Sydney. His qualifications extend to a Graduate Certificate in Management. He is also a past Honorary Treasurer of Scientists in Reproductive Technology.

A/Prof. Bakos has won a number of scientific awards both nationally and internationally, including the Society for Reproductive Biology Oozoa Award, the American Society for Reproductive Medicine Travelling Scholar Award. In 2019 he was awarded the Fertility Society of Australia Geoff Driscoll Medal.

July 2020 – June 2021 Research Projects

Ongoing research

Neurophysiology of cognitive behavioral therapy, deep breathing and progressive muscle relaxation used in conjunction with assisted reproductive technology treatments

A/Prof Hassan Bakos[1] and Dr Georges Raad[2]

[1]Monash IVF Group NSW, [2]Al-Hadi Laboratory and Medical Centre, Beirut, Lebanon

It has been recommended recently that psychosocial support should be offered as a complementary therapy during infertility treatments. In this effect, the efficiency of different psychological interventions, such as cognitive behavior therapy (CBT), deep breathing (DB), and progressive muscle relaxation (PMR), was evaluated in the context of ART treatment.

Applying these techniques was associated with mood improvements and a decline in stress biomarkers, and, hypothetically, reducing stress biomarkers associated with ART treatment. Accordingly, this study will ensure that these interventions reach their full potential and therefore improve clinical outcomes.

The impact of four sperm preparation techniques on sperm quality

A/Prof Hassan Bakos[1] and Dr Georges Raad[2]

[1]Monash IVF Group NSW, [2]Al-Hadi Laboratory and Medical Centre, Beirut, Lebanon

Current methods for the selection of sperm for IVF and ICSI remain relatively under-researched and there is little known about the impact of these methods on the molecular health of sperm. In particular, sperm with high levels of DNA damage are known to be associated with poorer pregnancy outcomes.

The aim of this study was to assess the impact of four sperm preparation techniques on sperm motility, sperm vacuoles, DNA fragmentation, intracellular ROS, acrosome reaction and mitochondrial activity. The results of the study will help optimize the existing sperm selection methods and establish an evidence-based approach to determine the safest methodology to select sperm for ART treatment.

Contributions to Scientific Literature

Peer Reviewed Journal Articles/Publications

1. Aitken RJ, Bakos HW. Should we be measuring DNA damage in human spermatozoa? New light on an old question. Hum Reprod. 2021 Jan; online doi:10.1093/humrep/deab004.
2. Raad G, Bakos HW, Bazzi M, Mourad Y, Fakih F, Shayya S, Mchantal L, Fakih C. Differential impact of four sperm preparation techniques on sperm motility, morphology, DNA fragmentation, acrosome status, oxidative stress, and mitochondrial activity: A prospective study. Andrology. 2021 May; 1-11.
3. Raad G, Tanios J, Azoyrt J, Daher A, Fakih C, Bakos HW. Neurophysiology of cognitive behavioural therapy, deep breathing and progressive muscle relaxation used in conjunction with ART treatments: a narrative review. Human Reprod Update. 2020 Sept; 1-15.

Presentations- National Conferences and Meetings

1. Bakos H. Sperm selection. SEED Meeting. 2021, May 22-23: Sydney, Australia.

Kuala Lumpur Research

Dato' Dr Prashant Nadkarni

MBBS (MAL), FRCOG (UK)

Medical Director & IVF specialist, KL Fertility Malaysia

Dr Prashant obtained his specialist qualification (MRCOG) in 1989 and chose to further sub-specialise in the field of infertility. He was fortunate to be selected to train with Prof Ian Craft, one of IVF's early pioneers. He spent the next two years (1989-1991) at the London Fertility & Gynaecology Centre in Harley St., where he was involved in cutting-edge infertility research and treatments which have now become a routine part of infertility management. Dr Prashant was seconded to Dubai to set up the centre from scratch. This fertility centre grew to become one of the largest fertility centres in the Middle East facilitating over 500 IVF and GIFT cycles a year.

Upon his return to Malaysia in 1997 he re-joined University Hospital and set up the IVF unit there. As Associate Professor, he was responsible for teaching students and resident doctors, and to this day, maintains an active interest in research and training. He is regularly invited to speak at public forums as well as at medical conferences on fertility issues.

On a national front, he is actively involved in helping to set standards in fertility practice and serves on several technical committees for the Ministry of Health, Academy of Medicine Malaysia, Ministry of Science, Technology & Innovation and the Malaysian Society for Quality in Health.

In recognition of his fertility-related work for the Tunku Azizah Fertility Foundation (TAFF) as well as his voluntary involvement at various national-level fertility initiatives, he was awarded a Dato' title by the Sultan of Pahang. He has also been awarded the Fellowship of the Royal College of Obstetricians & Gynaecologists in the UK.

Contributions to Scientific Literature

Peer Reviewed Journal Articles/Publications

1. Keen SP, Yeong TH, Siew-Keah L. Semen parameters in male partners of infertile couples in Malaysia. Medical Journal of Malaysia. 2019; 74 (1).

Presentations- International Conferences and Meetings

1. Tham MY, Chong MK, Lee SK, Sim PK, Loke MK, Nadkarni P. Is there an association between semen volume and age? Obstetrics & Gynaecology Society of Malaysia (OGSM). 2021 July 23 – 25; Online conference.
2. Tham MY, Chong MK, Lee SK, Sim PK, Loke ML, Nadkarni P. Comparison of post-thaw motility wth two different cryopreservation media. Obstetrics & Gynaecology Society of Malaysia (OGSM). 2020 May 29 – June 2; Online conference.

Poster presentations and Abstracts- International Conferences and Meetings

1. Sim PK, Nadkarni P. Is spontaneous ovulation better than induced ovulation for frozen-thawed embryo transfer cycle? ESHRE 37th Annual meeting; 2021 June 26- July 1; Online conference.

Monash & Sydney Ultrasound for Women

A/Prof Simon Meagher

BSc (Hons), MB BCH BAO, FRCPI, FRCOG, FRANZCOG, DDU, COGU

Medical Director of Monash Ultrasound for Women, Victoria; Lecturer, Monash University

As Medical Director of Monash Ultrasound for Women, Dr Simon Meagher oversees a team of 50 sonologists, sonographers, genetic counsellors, phlebotomists and administrative staff in delivering a tertiary level ultrasound service across south east Melbourne. Dr Meagher has dedicated 25 years of his term as Director, teaching and lecturing in obstetric and gynaecological ultrasound both locally and overseas.

In 2015 he was awarded 'Sonologist of The Year' by the Australian society of Ultrasound in medicine (ASUM) in recognition of his commitment to hands-on training within the hospital setting at the Mercy Hospital for Women, and his commitment and contributions to ASUM and the International Society of Ultrasound in Obstetrics and Gynaecology.

Dr Meagher has delivered over 700 lectures, across 15 countries, and 40 cities worldwide. He has conducted predominantly clinical research in obstetric ultrasound, with a focussed interest in early pregnancy screening and diagnosis. He has published 70 articles in peer review journals, including 15 in the last 3 years focusing on first trimester pregnancy screening and diagnosis. Dr Meagher has described five original sonographic fetal markers during the first and second trimesters of pregnancy. He is now focusing his interest on aneuploidy and embryo development from seven to 10 weeks as we approach the dawn of a new era of genetic screening via free fetal DNA analysis.

Dr Meagher has taken on multiple leadership positions - early in his career as the Chair of the Standards of Practice Committee at ASUM, examiner and executive board member for the ASUM Diploma of diagnostic ultrasound, and later as council member of ASUM. Thereafter he served as Chairman of the Victoria Obstetric Sonologists group and on several task force and education committees at the International Society of Ultrasound in Obstetric and Gynaecological Ultrasound. Dr Meagher is consultant sonologist at the Perinatal department, Mercy Hospital for Women, Melbourne.

Dr Melody Menezes

BSc(Hons), GDipGenetCouns, PhD, FHGSA

Scientific Director at Monash Ultrasound for Women

Melody is the Head Genetic Counsellor and Scientific Director at Monash Ultrasound for Women. She is also a Senior Lecturer at the University of Melbourne for the Master of Genetic Counselling and Master of Genomics and Health courses, and an Editor of the Journal of Genetic Counselling.

Melody's research and clinical interests include prenatal screening and testing, disability issues, and the ethical, legal and social aspects of genetic testing. She has a particular interest in Non-Invasive Prenatal Testing (NIPT) and has a number of publications looking at NIPT in the Australian population.

A/Prof Andrew McLennan

BSc MB BS (Hons) FRANZCOG MRCOG COGU

Clinical Associate Professor, Department of Obstetrics, Gynaecology and Neonatology, Northern Clinical School, Obstetrician Gynaecologist Sonologist, Sydney Ultrasound for Women

Associate Professor Andrew McLennan is a specialist obstetrician and gynaecologist whose particular interest is in prenatal diagnosis and ultrasound. He is a consultant to the Maternal Fetal Medicine Unit at Royal North Shore Hospital, a Clinical Associate Professor at the University of Sydney, and a Sonologist at Sydney Ultrasound for Women.

In a national first, Andrew introduced Nuchal Translucency (NT) screening for Down syndrome to Australia, helping to revolutionise the way prenatal screening for chromosome abnormality is conducted. He is the founding Chairman of the National Early Pregnancy Assessment Program and the past President of the Australian Association of O&G Ultrasonologists.

Andrew has been involved in educating doctors and sonographers in Australia and South-East Asia in the conduct of early pregnancy screening for fetal chromosome abnormalities and adverse pregnancy outcomes. He is actively involved in research into early diagnosis of fetal abnormalities and quality assurance in ultrasound.

July 2020 – June 2021 Research Projects

Completed research

Non-invasive prenatal testing with cell-free DNA for fetal trisomies 21, 18 and 13, in an ART population.

Dr Fabricio Costa[1], Andrew McLennan[2], Dr Simon Meagher[1], Dr Melody Menezes[1], Prof Jon Hyett[3]

[1]Monash Ultrasound for Women, Clayton; [2]Sydney Ultrasound for Women, Burwood; [3]Royal Prince Alfred Hospital, Sydney

ART pregnancies have reduced first trimester combined screening (FTCS) PAPP-A levels leading to an increased likelihood of receiving a false-positive result. Non-invasive prenatal testing (NIPT) is a recently available advanced screening test which involves testing cell-free DNA (cfDNA) in the maternal plasma. These cells are released from the placenta (fetal genetic material) into the maternal circulation and this allows the detection of common autosomal trisomies (21, 18, and 13) with a high level of accuracy in singleton pregnancies.

The objective of this study is to assess the performance of screening by NIPT for trisomies using a chromosome-selective sequencing method of cfDNA in maternal plasma obtained from an ART population undergoing routine screening at 11-13 weeks' gestation. A prospective chart review will be conducted to collect clinical data on patients who will have undergone combined FTCS and NIPT. From the 300 patients studied a high risk on FTCS is expected in 24-30 cases (~8-10%). We will compare the risk scores, between FTCS and NIPT.

The establishment of a normal range of embryonic heart rates in IVF pregnancies at seven weeks' gestation in an Australian population: embryonic heart rate as a determinant of first trimester loss

Presanna Sujenthiran[1], Dr Martha Finn[1], Dr Simon Meagher[1], Paul Lombardo[2]

[1]Monash Ultrasound for Women, Richmond; [2]Dept. Medical Imaging and Radiation Sciences, Monash University

ART births now account for ~3.6% of Australian births with almost 10,000 born each year. The 7 week ultrasound has become a definitive time to confirm a live intrauterine gestation for ART patients and it is therefore crucial to have established ultrasound parameters at this gestation. The boundary between normal and slow early embryonic heart rate (EHR) has not been well established in ART pregnancies.

The study aims to establish a normal range of embryonic heart rates at 7 weeks gestation in ART singleton pregnancies as well as to analyse whether the EHR between 6W1D (i.e. 6 weeks and one day) and 7W6D in singleton ART pregnancies is useful in predicting the likelihood of first trimester loss. The range of EHRs will be evaluated to determine whether they form a normal distribution. The primary outcomes include successful first trimester pregnancies, confirmed by the standard 12 week ultrasound examination or miscarriage confirmed by ultrasound or medical documentation.

PeTALS: A longitudinal study exploring women's experiences following a prenatal diagnosis of fetal abnormality

Dr Melody Menezes[1], Professor Sylvia Metcalfe[2], Dr Jan Hodgson[2], Professor Jane Fisher[3], A/Prof Kerry Petersen[4], A/Prof Jane Halliday[2]

[1]Monash Ultrasound for Women, Richmond; [2]Murdoch Children's Research Institute, Parkville; [3]Jean Hailes Clinical Research Unit, Monash University, Clayton; [4]School of Law, La Trobe University, Melbourne

Advances in genetic technologies are rapidly expanding the availability and accuracy of prenatal tests. In Australia, ~4% of babies are born with a fetal abnormality, many of which are diagnosed during pregnancy. Our multidisciplinary team will use a collaborative approach to understand how pregnant women are cared for following the diagnosis of a fetal abnormality, and to develop appropriate evidence-based models of supportive care. This study will be the first in Australia to investigate women's experiences of a prenatal diagnosis (PND) of fetal abnormality immediately following diagnosis. The study aims to (1) explore the psychosocial impact of a PND of fetal abnormality on women; (2) identify the social and professional supports utilised and needed by women and (3) describe the longer-term outcomes for women who receive a diagnosis of a fetal abnormality. The project will add to the existing knowledge in this under-researched field and contribute directly to improving the social and clinical care of women together with the education of the health professionals who care for them.

Reproducibility of three-dimensional ultrasound of the junctional zone in myometrial pathology and their correlation with pregnancy rates

Dr Lufee Wong[1,2], A/Prof Fabricio Costa[1,2], Prof Luk Rombauts[2,3], Prof Beverley Vollenhoven[2,3], Dr Hugo Fernandes[2,3,4], A/Prof Martin Healey[3,4], A/Prof Evdokia Dimitriadis[5], A/Prof Wellington Martins[6]

[1]Monash Ultrasound for Women, Richmond; [2]Monash Medical Centre, Clayton; [3]Monash IVF, Clayton; [4]The Royal Women's Hospital, Parkville; [5]Hudson Institute, Clayton; [6]Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Brazil

During pregnancy, the endometrial-myometrial junction, or junctional zone (JZ), is fundamental to the process of implantation and placentation. Consequently, any myometrial disorders, such as adenomyosis, can disrupt the process, leading to infertility and various pregnancy complications. While magnetic resonance imaging (MRI) can be used in the assessment of the JZ, it is not readily available, expensive and can be claustrophobic for some patients. Three-dimensional (3D) ultrasound has made it possible to assess minor changes in the JZ. A consensus statement in 2015 on the classification system of myometrial disorders aims to assess the JZ using standardised nomenclature.

This study aims to assess the reproducibility of this evaluation of the JZ using 3D-ultrasound, as well as the correlation of the JZ changes with pregnancy rates. Being able to accurately determine adenomyosis will help in the diagnosis and counseling of patients with infertility before undergoing IVF cycles. Furthermore, recent studies have identified that small non-coding RNA, microRNA (miR), are differentially expressed in human endometrium across the menstrual cycle suggesting they are hormonally controlled.

Uterine miR expression levels are altered in a number of uterine disorders and a recent study demonstrated that miR levels in human endometrium correlate with serum levels in women with primary infertility. We propose that, similarly, miR levels in serum may reflect alterations in the JZ and may be useful in the diagnosis of adenomyosis in conjunction with 3D-ultrasound..

July 2020 – June 2021 Research Projects

Ongoing research

Performance and characteristics of non-invasive prenatal testing (NIPT) in assisted reproductive technology (ART) conceptions

Dr Melody Menezes[1,2], Mr Tim Lee[3], Prof Jane Halliday[2,4], A/Prof Lisa Hui[2,4,5], Dr Sharon Lewis[2,4], A/Prof Fabricio da Silva Costa[1,3,6]

[1]Monash Ultrasound for Women, Clayton; [2]Murdoch Children's Research Institute, Parkville; [3]Monash University, Clayton; [4]The University of Melbourne, Parkville; [5]Mercy Hospital for Women, Heidelberg; [6]Monash Medical Centre

During pregnancy small fragments of cell-free DNA (cfDNA) from both mother and fetus circulate in maternal peripheral blood. Non-Invasive Prenatal testing (NIPT) analyses these cfDNA fragments to screen for the most common chromosome conditions in pregnancy (i.e. Trisomy 21 (Down syndrome), Trisomy 18 (Edward's syndrome), Trisomy 13 (Patau syndrome) and sex chromosome aneuploidy). To date, Monash Ultrasound for Women (MUFW) has screened over 7000 pregnancies with NIPT; approximately 20% of which are ART conceptions. Despite the high uptake of NIPT among women with ART conceptions, there is currently no reliable performance data or evidence to support the use of NIPT in this particular population.

As leaders in the field of IVF, and recently having developed NIPT within the Monash IVF group, we are in the unique position of having fertility, ultrasound and NIPT data for all our patients. It is a known challenge for researchers to ensure complete clinical follow up of cases, in particular, identifying false negative cases of NIPT. Victoria is in a unique position to perform complete follow-up due to existing pre- and post-natal databases. Generating evidence on the performance of NIPT in the ART population will allow the Monash IVF group to play an important role in evidence-based practice and innovation in this rapidly advancing area.

Validation of prospective first trimester screening for preterm preeclampsia in the Australian population

Dr Daniel Lorber Rolnik[1], A/Prof Fabricio da Silva Costa[1,2], A/Prof Andrew McLennan[3]

[1]Monash Health, Clayton; [1,2]Monash Ultrasound for Women, Clayton; [3]Sydney Ultrasound for Women, Sydney

Despite all the research published in the last three decades on screening and prevention of preeclampsia, the condition remains as one of the main causes of maternal and perinatal morbidity and mortality worldwide. It affects 2-8% of all pregnancies and it is responsible for one out of five maternal deaths and 15% of the premature deliveries. This research aims to assess and validate in the Australian population a previously published first trimester algorithm for prediction of preeclampsia that combines maternal characteristics, uterine artery Doppler, mean arterial pressure and biochemistry (pregnancy associated plasma protein-A - PAPP-A - and placental growth factor - PlGF). This algorithm detects 75-80% of all cases of preeclampsia requiring premature delivery and more than 90% of the cases that will require delivery before 34 weeks, with a false-positive rate of 10%. The algorithm was recently evaluated in a European multicentre prospective study and seems to be far superior than screening by maternal factors alone. However, there is only one study validating this predictive test in the Australian population and no studies adding PlGF to the algorithm.

First trimester screening for preterm preeclampsia is routinely offered as part of the 11-14 weeks' ultrasound at Monash Ultrasound for Women (MUFW) and at Sydney Ultrasound for Women (SUFW) and more than 20,000 women were prospectively screened since June 2013 in both services. Furthermore, recent clinical trials and meta-analyses have shown that initiation of low-dose aspirin before 16 weeks for patients at high risk reduces by more than 60% the incidence of preterm preeclampsia.

Contributions to Scientific Literature

Peer Reviewed Journal Articles/Publications

1. Ekelund CK, Rode L, Tabor A, Hyett J, McLennan A. Placental growth factor and adverse obstetric outcomes in a mixed-risk cohort of women screened for preeclampsia in the first trimester of pregnancy. Fetal Diagn Ther. 2021 Mar; 48(4): 304-312.
2. Hui L, Pynaker C, Bonacquisto L, Lindquist A, Poulton A, Kluckow E, Hutchinson B, Norris F, Pertile MD, Gugasyan L, Kulkarni A, Harraway J, Howden A, McCoy R, da Silva Costa F, Menezes M, Palma-Dias R, Nisbet D, Martin N, Bethune M, Poulakis Z, Halliday J. Reexamining the optimal nuchal translucency cutoff for diagnostic testing in the cell-fre DNA and microarray era: results from the Victorian Perinatal Record Linkage study. Am J Obstet Gynecol. 2021 May.
3. Menahem S, Sehgal A, Meagher S. Early detection of significant congenital heart disease: The contribution of fetal cardiac ultrasound and newborn pulse oximetry screening. J Paediatr Child Health. 2021 Mar; 57(3):323-327.
4. Mogra R, Saaid R, Rooher J, Pedersen K, Kesby G, Hyett J. Prospective validation of first-trimester ultrasound characteristics as predictive tools for twin-twin transfusion syndrome and selective intrauterine growth restriction in Monochorionic Diamniotic twin pregnancies. Fetal Diagn Ther 2020; 47: 321-327.
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7. Ramkrishna J, Menezes M, Humnabadkar K, Tse C, Maxfield MJ, da Silva Costa F, Rolnik DL, Meagher S. Outcomes following the detection of fetal edema in early pregnancy prior to non-invasive prenatal testing. Prenat Diagn. 2021 Jan; 41(2): 241-247.
8. Sandow R, Scott FP, Schluter PJ, Rolnik DL, Menezes M, Nisbet D, McLennan AC. Increasing maternal age is not a significant cause of false positive results for monosomy X in non-invasive prenatal testing. Pren Diag. 2020 Oct; 40(11): 1466-1473. 2020 Sept; 2(3): 96-101.
9. Sekhon J, Lee E, Lo G, Woolcock J, Ramkrishnan J, Menezes M, Tan S, Meagher S, Murphy A. Lipiodol flush under ultrasound guidance in Australia. 2020 Dec; 60(6): 965-969.
10. Sepulveda W, Bornstein E, Andreeva E, Montano I, Gutierrez J, Martinez-Ten P, Meagher S. First-trimester sonographic diagnosis of sirenomelia: A multicenter series of 12 cases and review of the literature. Prenatal Diagnosis. 2020 Feb; 40(5): 626-634.
11. Smet ME, Scott FP, McLennan AC. Discordant fetal sex on NIPT and ultrasound. Prenatal Diagnosis. 2020 Oct; 40(11): 1353-1365.
12. Wertaschnigg D, Reddy M, Ramkrishna J, da Silva Costa F, Sepulveda W, Rolnik DL. Ultrasound appearances of the Acrania-Anencephaly sequence at 10 to 14 weeks' gestation. Journal of Ultrasound in Medicine. 2020 Mar; 39(9): 1695-1700.
13. Wertaschnigg D, Reddy M, Ramkrishna J, da Silva Costa F, Sepulveda W, Rolnik DL, Meagher S. Ultrasound appearances of the Acrania-Anencephaly sequence at 10 to 14 Week's gestation. J Ultrasound Med. 2020 Sep; 39(9):1695-1700.


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