

MONASH IVF RESEARCH
AND EDUCATION FOUNDATION



2014

2014

ANNUAL REPORT



2014

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MONASH IVF RESEARCH AND EDUCATION FOUNDATION

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EXCELLENCE IN RESEARCH AND EDUCATION

MONASH IVF HAS LONG RECOGNISED THE CLOSE LINKAGE BETWEEN RESEARCH AND BEST CLINICAL PRACTICE AND CONTINUES TO BE ACTIVELY ENGAGED IN RESEARCH AND POSTGRADUATE MEDICAL EDUCATION IN REPRODUCTIVE MEDICINE.

Monash IVF Research and Education Foundation (MREF)

Since 2009, the Monash IVF Research and Education Foundation (MREF) has been operating under the oversight of an Advisory Board and with the assistance of a committed team of researchers and educators. The historical and vital relationship with Monash University is maintained through the inclusion of a senior University member on the MREF Advisory Board and by the conduct of joint postgraduate educational programs.

The MREF advises the Medical Advisory Committee, and thence the Monash IVF Group Board, on ways in which Monash IVF can conduct internationally-recognised research, provide educational programs for health professionals and raise community awareness and knowledge in reproductive medicine.

The focus of our studies in ART is the effectiveness and safety of our treatments for couples and their offspring. Major recipients of the research funding include investigators at the Monash University Departments of Obstetrics and Gynaecology, the School of Biological Sciences, and the MIMR-PHI Institute and the Murdoch Institute.

Joint educational activities with the University's Education Program in Reproductive Biology (EPRD) include participation in EPRD's renowned reproductive science courses, along with specialised courses for postgraduate medical education for local and overseas clinicians. Recognising the key roles of embryology, nursing and allied staff to the success of our ART program, innovative educational programs have also been developed for these groups.

With the formation of the Monash IVF Group in June 2014, the research skills and resources of the Repromed program and its affiliates at the University of Adelaide, has broadened the opportunities for research. An Executive of MREF and the Repromed research teams has been formed to set Group-wide research and development objectives, to ensure increasing collaboration and the optimal use of resources, particularly in clinical trials aiming to improve success rates.

This report includes the research and educational outputs from MREF Advisory Board members and other Monash IVF staff in regard to their work both at Monash IVF and within their professional spheres, in the field of reproductive medicine and fertility control over the 2014 calendar year.

COMMENT FROM THE GROUP CEO

(on behalf of the Board)

James Thiedeman | Group Chief Executive Officer, Monash IVF

THE EARLY WORK OF OUR PIONEERS THAT RESULTED IN THE WORLD'S FIRST IVF PREGNANCY IN 1973 HAS BEEN AN ONGOING DRIVER FOR OUR COMMITMENT TO CONTINUED SCIENTIFIC AND CLINICAL INNOVATION. AS TESTAMENT TO THIS COMMITMENT STANDS OUR LONG HISTORY OF INVESTING IN CLINICAL RESEARCH AND EVIDENCE-BASED CARE.

Since inception, the Monash IVF Research and Education Foundation (MREF) has overseen intramural and collaborative research programs in the fields of male and female reproductive biology and clinical care, genetics and molecular science and psychosocial research. This work endeavours to advance patient-focused assisted reproductive technologies.

Our latest report highlights the achievements of our clinical, scientific and research team, including attaining several awards at the 5th congress of the

Asia Pacific Initiative on Reproduction (ASPIRE) held in conjunction with the Fertility Society of Australia (FSA) Annual Scientific Conference.

In addition to conducting original research, Monash IVF Group is committed to training the next generation of professionals in the field of assisted reproduction. Through MREF, we continue to dedicate resources to the Royal Australian and New Zealand College of Obstetricians and Gynaecologists' (RANZCOG) subspecialty training programs and work hand-in-hand with Monash University's Education Program in Reproduction and Development (EPRD) and the University of Adelaide. We are most grateful to our clinicians and scientists for the time and expertise they impart on these educational activities.

Monash IVF Group understands our commitment to ongoing scientific and clinical innovation, combined with the development of future leaders in the field, will ultimately benefit women and couples pursuing their dream of creating a family of their own. On behalf of the Monash IVF Group Board, I commend the work of the MREF and express my thanks to all our staff and collaborators involved in this important work.



MEDICAL DIRECTOR'S REPORT

Associate Professor Peter Lutjen | National Medical Director, Monash IVF

MONASH IVF CONTINUES ITS LONG-TERM COMMITMENT TO EXCELLENCE IN SCIENTIFIC RESEARCH AND CLINICAL TRAINING IN THE AREA OF ARTIFICIAL REPRODUCTIVE TECHNOLOGIES (ART). IT IS THIS COMMITMENT THAT ULTIMATELY TRANSLATES INTO THE BEST POSSIBLE CLINICAL SERVICES FOR OUR PATIENTS.

With ongoing investment in translational research programs, Monash IVF continues to gain valuable insight into areas of basic reproductive biology that can be extended into our daily clinical practice. It is this form of innovation that is reflected in our clinical services and translates into improved outcomes for our patients.

These activities necessitate not just the work of our own research and clinical staff but also the existence of active collaborations with other research experts in these areas. The governance for these activities falls to the Monash

Research and Education Foundation (MREF). The Foundation advises the Monash IVF Board through the Medical Advisor Committee (MAC) on the areas of research which have the potential to improve the organisation's clinical care and allocates research funds accordingly. Areas of research activity include examining aspects of endometrial receptivity, the genetic causes of infertility, optimizing selection of sperm, eggs and embryos, and the outcomes for children born to IVF.

The MREF helps maintain the strong historic affiliation between Monash IVF, Monash University and MIMR-PHI Institute. In addition to the collaborative research between these three organisations, the MREF helps coordinate educational programs to help train the future leaders in ART for work in the area both here in Australia and overseas, thereby making a valuable contribution to improving clinical service delivery.



A WORD FROM THE CHAIRMAN OF THE MREF

Professor Robert McLachlan | Chairman, Monash Research & Education Foundation

THE EXCELLENCE OF THE CLINICAL SERVICES AT MONASH IVF HAS ITS FOUNDATION IN THE CONTINUOUS RESEARCH EFFORTS OF OUR SCIENTIFIC AND CLINICAL STAFF OVER THE PAST 40 YEARS.

The Monash IVF Group has an ongoing commitment to original research and educational programs and to maintaining its leadership position in ART. I have been honoured to serve as the inaugural Chairman and to have received the strong and continuing support of the Monash IVF Board and CEO. We are also excited to have had Dr Michelle Lane and the Repromed program and its network of co-investigators at the University of Adelaide strengthen the research capabilities of the Monash IVF Group. We continue to be supported by both the Monash IVF Group and by generous untied research grants from industry.

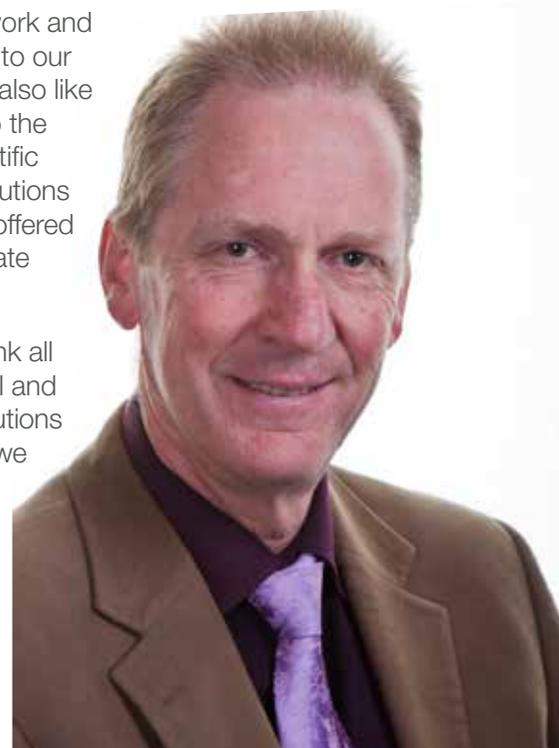
The MREF Advisory Board comprises clinical, embryological and medical imaging expertise and has worked with enthusiasm and creativity to develop programs that address our strategic goals. The outcomes of papers and presentations for 2014 and our future research directions are outlined in this report.

I am most grateful to Associate Professor Luk Rombauts, Director of Clinical Research, for his dedication and expertise in the conduct of our many clinical studies, and to Dr Tiki Osianlis, Scientific Director and her team, for their enthusiastic engagement in 'in house' and collaborative research programs aimed at understanding embryo health and implantation.

Our work is only possible with the help of our dedicated research team: Caroline Motteram, Scientific Projects Officer; Deborah de Guingand, Research Officer, and Vivien MacLachlan, Data and Research Manager. They have tirelessly and diligently overseen the clinical studies, working with our study participants, and dealing with complex interactions with the medical nursing and scientific staff.

In 2014 our education program saw the continuation of the alliance between the Monash University EPRD and MREF with many shared programs and the hosting of several overseas clinicians and scientists for short course updates in ART. We are most grateful to Dr Sally Catt and the EPRD staff for the excellent work and enthusiasm and look forward to our future collaborations. I would also like to express my appreciation to the Monash IVF clinical and scientific staff for their excellent contributions to the educational programs offered to undergraduate, postgraduate and overseas trainees.

Finally I would also like to thank all the Monash IVF Group clinical and scientific staff for their contributions to the educational programs we provide to undergraduate, postgraduate and overseas trainees.



MONASH IVF RESEARCH AND EDUCATION FOUNDATION ADVISORY BOARD



Professor Robert McLachlan MBBS (Hons), PhD, FRACP

Chairman MREF, Director of Clinical Research, MIMR-PHI Institute; Adjunct Professor, Monash Department of Obstetrics and Gynaecology; Director, Andrology Australia; 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, working on the hormonal regulation of reproductive function. After returning to Australia in 1990, he has since attracted continuous funding as a Research Fellow of the NH&MRC.

He is an Adjunct Professor in the Department of Obstetrics and Gynaecology at Monash University. As Director of Clinical Research at the MIMR-PHI Institute at Monash Medical Centre, he conducts NHMRC supported research involving

basic and clinical research into male fertility regulation and the role of androgens. He has published over 200 papers, reviews and chapters. Since 2000, he has made 53 international & 40 national presentations (including keynotes & plenaries). He is Section Editor "Male Endocrinology" for www.ENDOTEXT.org; and is on several editorial boards, and is a consultant on male fertility regulation to the World Health Organisation. In 2013 he was awarded the Hoffenberg International Medal, Society for Endocrinology, UK, for outstanding contributions to the field.

Professor Rob McLachlan 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 and Deputy Director of Endocrinology, Monash Medical Centre. He is a Past President of the Fertility Society of Australia and is currently a Consultant to the World Health Organisation on male fertility regulation and is Director of Andrology Australia, a Federal government initiative, based at Monash University, which is committed to research and community and professional education in male reproductive health.



Associate Professor **Luk Rombauts** PhD, MD, FRANZCOG, CREI

Research Director, Monash IVF; Clinical Adjunct Associate Professor, Department of Obstetrics and Gynaecology, Monash University; Head of Reproductive Medicine, Monash Health; IVF Specialist, Monash IVF

Trained in obstetrics and gynaecology at the University of Leuven, Belgium, in 1994, Assoc Prof Rombauts began his clinical and research work at Monash in 1994. After spending a further 2 years in the IVF unit at the Leuven Institute of Fertility and Embryology (Belgium), Assoc Prof. 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.

Assoc Prof. 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. Assoc Professor Luk Rombauts has published a total of 115 articles, reviews and book chapters since 1990. He has a current h-index of 21 (Web of Knowledge 2014) and 1348 total 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 Associate Professor in the Department of Obstetrics and Gynaecology at Monash University and the Head of Reproductive Medicine at Sothern Health. He is the Clinical Research Director of Monash IVF and a Research Fellow of the MIMR-PHI Institute. Assoc Prof Rombauts was elected a Board Member of the World Endometriosis Society in 2008 and is the editor of the World Endometriosis Society's electronic journal. In 2011 he was appointed to the World Endometriosis Research Foundation Board of Trustees and to the Board of the Fertility Society of Australia. He is also a member of the RANZCOG Grants and Scholarship Committee. He is an associate editor of Human Reproduction and has been the Scientific Chair of 2 international conferences.

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



Dr Tiki Osianlis
BSc (Hons), PhD

Scientific Director, Monash IVF, Scientific Advisor MREF

Dr Osianlis completed her Bachelor of Science (Hons) at Monash University and went on to complete her PhD with IVF pioneer Professor Alan Trounson. Her studies focused on examining the physiological mechanisms of a select group of antigens during fertilisation and preimplantation development. She has been with Monash IVF since 1997 and is the current Scientific Director. Dr Osianlis is responsible for the Embryology and Genetics laboratories within Monash IVF and oversees operational performance, auditing and training compliance, quality management and implementation of new technologies. She is dedicated to achieving optimal results and increasing success rates. Her main research interests

are in gamete and embryo cryopreservation, sperm-oocyte interaction during fertilisation, optimal embryo selection, blastocyst-endometrial interaction and the relationship of stimulation regimen and embryo quality.



Associate Professor Beverley Vollenhoven
MBBS (Hons), PhD,
FRANZCOG, CREI

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

Associate Professor Vollenhoven graduated from Monash University in 1984 and completed her training in Obstetrics and Gynaecology in 1995. She has been a clinician at Monash IVF since 1996 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); the management of infertility, particularly IVF, ovulation and ovulation disorders (such as PCOS), Turner's Syndrome and menopause. She has more than 100 publications in both journals and books.

Associate Professor Vollenhoven is the Head of Gynaecology at Monash Health and also of the Contraceptive Counselling Clinic and a Reproductive Endocrinologist at the Menopause Clinic, Monash Medical Centre.

She is a Past Chairperson of the Victorian Regional Committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and is a member of the Examinations Committee and is currently an examiner for both the specialist and sub specialist exams. She was a member of the 8th Council of RANZCOG. She is a member of the Advisory Committee on Prescription Medicines as well as the Device Committee, both subcommittees of the TGA. Associate Professor Vollenhoven was appointed Director of Teaching and Learning, MREF in June 2012.



Dr Fabricio Costa
MD, PhD, FRANZCOG, DDU,
COGU

Obstetrician Sonologist, Monash
Ultrasound for Women

Associate Professor Costa graduated in Medicine in 1995. He was awarded a PhD in 2001 from the University of Sao Paulo, Brazil for Doppler studies in the prediction of pre-eclampsia. In 2005, A/Prof Costa became an Associate Professor in Obstetrics and Gynaecology and in 2014, he became Clinical Associate Professor in the Department of Obstetrics and Gynecology at the University of Melbourne. In 2009, A/Prof Costa moved to Australia, currently working at the Royal Women's Hospital (University of Melbourne Department of Obstetrics and Gynaecology) and Monash Ultrasound for Women in Melbourne.

A/Prof Costa has strong academic credentials having published widely, including several chapters in various texts, and performs peer reviews for many international journals including Fetal Diagnosis and Therapy, Clinical Anatomy and

Journal of Perinatal Medicine. A/Prof Costa's clinical and research interests focus on the use of ultrasound in maternal-fetal medicine, especially pre-eclampsia, fetal growth restriction and preterm labour. In addition, he has special interest in first trimester screening, including non-invasive prenatal testing (NIPT), and ultrasound diagnosis of deep endometriosis.



Dr Gareth Weston MBBS
(Hons), MPH, PhD, FRANZCOG,
CREI

Senior Lecturer in the Department of Obstetrics and Gynaecology at Monash University; IVF Specialist and Clinical Director Sunshine and Gippsland, Monash IVF

Dr Gareth Weston graduated from Melbourne University in 1996. He completed a PhD in reproductive medicine and molecular biology in 2003, spending time at Cambridge University UK. He completed a Masters in Public Health in 2002. He also completed a sub-specialty qualification in Reproductive Endocrinology and Infertility (CREI) in 2007. He holds public appointments at Monash Medical Centre and Bairnsdale Regional Hospital.

Dr Weston has published more than 40 book chapters and journal articles, and is the author of a textbook on exam preparation for gynaecology trainees. Dr Weston has a wide range of clinical and research interests including conservative infertility treatments, IVF, egg freezing for medical and social reasons, donor sperm infertility treatment for lesbian and single women, endometriosis, PCOS, and fibroids.



Royal Australasian College of Physicians. Following a term as the 28th Governor of Victoria from 2006 to 2011 he has returned to pursue research as a Sir John Monash Distinguished Professor.

His reproductive research program encompasses genetic causes of male infertility, control systems involved in ovulatory mechanisms and exploring novel causes of developmental abnormalities of the genitalia. He also has a program of research designed to develop treatments for inflammatory diseases such as cystic fibrosis and acute lung injury, involving the activins and follistatin, with major long-term implications for patients. He also has an interest in community and professional education in male reproductive health.

Prof David de Kretser AC

MBBS, MD, FRACP, FAA, FTSE,
Hon LLD (Monash), Hon LLD
(Melbourne), FRANZCoG (Hon),
FRCOG (Hon)

Distinguished Sir John Monash Professor,
Centre for Reproductive Health, MIMR-PHI
Institute of Medical Research

Professor de Kretser is reproductive endocrinologist whose appointments at Monash have included Professor of Anatomy, the founding Director of the Monash Institute of Medical Research and the Associate Dean for Biotechnology Development. He is a Fellow of the Australian Academy of Science, a Fellow of the Australian Academy of Technological Sciences and Engineering and a Fellow of the

A WORD FROM THE DIRECTOR OF EDUCATION

Associate Professor Beverley Vollenhoven

OUR PARTNERSHIP WITH MONASH UNIVERSITY'S EDUCATION PROGRAM IN REPRODUCTION AND DEVELOPMENT (EPRD) CONTINUES TO DEVELOP.

Clinicians and embryologists provide teaching for both the Diploma and Masters courses, and in 2014 there was a further collaboration not only in teaching but also in research. The Monash Observership Program also continued in 2014. We trained clinical specialists from Mexico and China. These were tailor made programs and will continue in 2015.



A WORD FROM THE DIRECTOR OF CLINICAL RESEARCH

Associate Professor Luk Rombauts



IT IS VERY PLEASING TO SEE HOW PRODUCTIVE THE MONASH IVF RESEARCH AND EDUCATION FOUNDATION HAS BEEN IN 2014.

The research team grows from strength to strength every year. My sincere thanks go out to Caroline Motteram, our dedicated research coordinator, who has been instrumental in keeping the ever growing number of projects that we now have in our research portfolio on track. I am also indebted to Deborah De Guingand whose contribution as a very experienced research nurse has been invaluable. My gratitude also goes out to Vivien MacLachlan. She is an irreplaceable member of the research team with her invaluable data management skills and perfect corporate memory.

2014 RESEARCH HIGHLIGHTS

“THE MREF STRIVES TO ENHANCE AND DEVELOP RESEARCH PROGRAMS THAT COMBINE FUNDAMENTAL SCIENCE WITH STRONG CLINICAL INTERACTIONS.”

This commitment to scientific development will ultimately lead to more safe and effective treatments for our patients. In 2014 our research program saw the continuation of our successful collaborations with the MIMR-PHI Institute and Monash University. These initiatives continue to make a valuable contribution to improving the understanding of embryo-endometrial interactions and egg and early embryonic development.

MREF also supported the participation of Monash IVF in a major study which appeared in the prestigious international journal, *Fertility and Sterility*. This study assessed the health and development of young adults conceived by assisted reproduction prior to 1992. The study was overseen by Professor Jane Halliday and colleagues at the Murdoch Children’s Research Institute, and involved investigators at Melbourne and Monash Universities, and Melbourne and Monash IVF. Overall ART offspring have grown into healthy young adults with a quality of life and educational achievement comparable to those of non-ART conceived peers.

In 2014 the MREF also successfully engaged in several clinical trials. We would like to thank our research support staff for their dedicated commitment to the LIGHT and BASIC studies both of which concluded in 2014. These projects strengthened our partnership with our collaborators at the University of Adelaide and Ferring Pharmaceuticals International. We also

welcomed Dr Shavi Fernando who will be investigating the clinical efficacy of melatonin supplementation in IVF as part of his PhD thesis.

Continuing our excellent record of research success, our researchers continue to have a strong presence at both local and international scientific meetings. In recognition of their achievements our researchers have received several awards at the 5th congress of the Asia Pacific Initiative on Reproduction (ASPIRE) which was held in conjunction with the FSA Annual Conference in Brisbane. We commend scientist Andrea Benz on receiving the prestigious ASPIRE award for Best Clinical Paper for her work on extended embryo culture. We would also like to congratulate scientist Ilona Rose who was awarded Best Clinical Paper for her investigation in to the increasingly used ‘freeze only’ strategy in IVF.

The MREF also supported several Medical student research placements from both local and international Universities. Under the direction of Professor Gab Kovacs, Dr Rosie Briggs, University of Edinburgh published her work on quantity of oocytes collected and IVF success rates in the esteemed *Journal of Human Reproduction*. Dr Emily Fiske, Monash University, Melbourne published her work on the utilisation of ART in single women and lesbian couples in the *Australian and New Zealand Journal of Obstetrics and Gynaecology*.

COMPLETED PROJECTS

Barusiban Subcutaneously for Reducing Implantation Failure Due to Uterine Contractions (The BASIC trial)

A/Prof Luk Rombauts

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Dr Alon Talmor

Monash IVF, Clayton

Dr Virochana Kaul

Monash IVF, Clayton

Dr Sameer Jatkar

Monash IVF, Clayton

Caroline Motteram

Monash IVF, Richmond

Deborah de Guingand

Monash IVF, Richmond

During a woman's menstrual cycle, the muscular tissue in her womb contracts with different frequency. Contractions may also be induced when the fertilised egg(s) is transferred to the womb in women undergoing infertility treatment. Excessive contractions at the time of transferring the fertilised egg(s) have been associated with a reduced chance of pregnancy. It is hypothesised that these contractions expel the fertilised egg(s) from the womb or prevent it from implanting. A reduction in contractions in the womb on the day of transfer may thereby increase the chance of pregnancy in IVF/ICSI patients.

Previous clinical trials have shown that Barusiban, a selective oxytocin antagonist, is able to reduce the frequency of contractions in the womb. The trial was the first using Ferring Pharmaceutical's drug Barusiban in IVF/ICSI patients who are having fertilised egg(s) transferred to the womb. The trial population included women with a history of several IVF/ICSI cycles that failed to result in a pregnancy. This multinational, multi-centre randomised controlled clinical trial aimed to determine the effect of Barusiban administered subcutaneously on the day of transfer on implantation and pregnancy rates in IVF/ICSI patients. The study was conducted for Ferring Pharmaceuticals, Copenhagen, Denmark.

Human Growth Hormone in management of poor responders (The LIGHT study)

Prof Robert Norman

Robinson Institute, The University of Adelaide

A/Prof Luk Rombauts

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Dr Gareth Weston

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Caroline Motteram

Monash IVF, Richmond

The ability of oocytes to form structurally normal embryos that are able to implant has been related to the concentration of hormones in ovarian follicular fluid. Growth hormone (GH) levels in blood have shown the most consistent relationship with parameters of embryo quality, with higher concentrations associated with rapid cleavage, better cleaving embryo morphology and higher embryo implantation potential. Furthermore follicular fluid GH concentrations decrease in women aged 40 years as compared with young women.

The rationale for recombinant Growth Hormone (r-GH) use is that it may potentiate the effect of the gonadotrophin treatment used in IVF. Growth hormone is reported to modulate the action of FSH on granulosa cells by up-regulating the local synthesis of insulin-like growth factor-I (IGF-I). This amplifies the effect of gonadotrophin action at the level of both the granulosa and theca cell. Overall, there is evidence for the use of rGH in the management of IVF cycles of poor responders but more research is needed. This multicentre randomised controlled clinical trial aimed to determine the effect of r-GH co-stimulation on live birth rates in poor responders undergoing an IVF/ICSI cycle. Recruitment for this project has now completed and the results will be presented at the Fertility Society of Australia annual scientific meeting 2015.

Defining the impact of different assisted reproduction technology (ART) protocols on the placental epigenome

Dr Stefan White

MIMR-PHI Institute of Medical Research, Clayton

A/Prof Luk Rombauts

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Prof Euan Wallace

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Although ART has become widely applied, some concerns have been raised about the effect ART might have on the offspring. These are based on findings of an increased risk of genetic imprinting disorders in children conceived by ART. Imprinting disorders are caused by epigenetic alterations, which are heritable changes in either DNA methylation or histone modifications. The effect of ART on the epigenetic status of the placenta has been relatively unexplored, although initial studies suggest that histone modifications may play a major role in the maintenance of imprinting.

In this study we combined next-generation sequencing technology with chromatin immunoprecipitation (ChIP-Seq) to study histone modifications in placentae derived from natural conceptions, and compare these with placentae derived from different ART protocols. If significant differences are found these will be followed up in a larger cohort of samples using targeted analysis, and the consequence of these epigenetic disturbances on gene expression will be measured. This study represents the first genome-wide study into the effects of different ART protocols on placental epigenetics. The results are currently being prepared for publication. It is anticipated that they will impact on future developments in ART procedures, and may lead to therapeutic interventions that eliminate any adverse effects ART may have on the epigenetic status of both the placenta and child.

Oocyte vitrification: IVF and pregnancy outcomes at Monash IVF

Janani Paramanatham

Monash University, Clayton

Dr Gareth Weston

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Dr Tiki Osianlis

Monash IVF, Clayton

Dr Alon Talmor

Monash IVF, Clayton

The initial success rates for oocyte cryopreservation were low due to the fragility of oocytes and their vulnerability to cellular disruption, but new freezing methods have led to better outcomes. Oocytes can be cryopreserved using either a slow freezing method, or a faster vitrification method. Slow freezing subjects oocytes to controlled cooling rates and less cryoprotectant substances, but has been associated with lower oocyte survival rates. Vitrification protocols however, use fast cooling rates combined with a higher concentration of cryoprotectant substances to prevent the formation of ice crystals within the oocytes. Ideally, this results in more viable oocytes after warming.

Given the emergence of these new procedures and the growing demand for frozen oocytes in IVF, research is needed to determine the feasibility of oocyte cryopreservation and its pregnancy outcomes in comparison with other procedures. This study investigated the utilisation of frozen oocytes in IVF and consequent pregnancy outcomes through a retrospective analysis fresh and VOT (vitrification oocyte thaw) cycles at Monash IVF. Among a diverse population of IVF patients of varied ages and clinical backgrounds using autologous oocytes, oocyte vitrification does not reduce the chances of pregnancy or adversely impact the gestational age and birth weight of babies born. Oocyte vitrification appears to be a viable option for many patients, providing good pregnancy outcomes and allowing the birth of healthy babies for these women.

Development of a diagnostic test to explore Chlamydia trachomatis tubal factor infertility in women

Dr Wilhelmina Huston

Queensland University of Technology, Kelvin Grove

A/Prof Luk Rombauts

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Dr Gareth Weston

Monash Dept Obstetrics and Gynaecology and Monash IVF, Clayton

Dr John Allan

Monash IVF, Wesley

Caroline Motteram

Monash IVF, Richmond

Deborah de Guingand

Monash IVF, Richmond

Chlamydia trachomatis is a bacterium that is spread by sexual contact. The infection is often asymptomatic. Once it is diagnosed the infection can be easily treated with antibiotics. However, in some women the infection will result in serious damage to the upper reproductive tract. In particular the infection and the resulting immune response can result in tissue scarring that blocks the fallopian tubes. The damaged tubes are routinely diagnosed by invasive medical procedures including laparoscopy or hysterosalpingography. While there are blood tests which claim to diagnose Chlamydia related tubal infertility in women, these are not routinely used due to poor reliability of the established tests.

We have recently developed a highly specific blood test for women who have confirmed tubal factor infertility (TFI) and due to Chlamydia trachomatis. In this pilot study we showed that this blood test outperforms the other leading tests in the diagnosis of Chlamydia-associated infertility. We plan to conduct a large national observational cohort trial to evaluate the test as part of the routine infertility workup in women in order to identify the subgroup that would be best fast-tracked to IVF treatment.

We are also recruiting further participants in new IVF clinics in order to validate the performance of the test. This prevents these women from requiring invasive procedures for diagnosis and speed up their fertility treatment journey.

A multi-clinic prospective study of participants engaging in a Victorian altruistic surrogacy program

Dr Celia Goncalves

Monash IVF, Clayton

Rita Alesi

Monash IVF, Clayton

Dr Sarah Phillips

Melbourne IVF, Melbourne

Marianne Tome

Melbourne IVF, Melbourne

A/Professor Jane Fisher

Monash University, Melbourne

The implementation of the Assisted Reproductive Treatment (ART) Act (2008) has resulted in significant changes to practices within ART clinics. One of these is the introduction of a legal framework for surrogacy arrangements. Recent research has focused on the experiences, characteristics and motivations of surrogates; parent-child relationships and disclosure to surrogate offspring; and changes in mood and trait profiles of the commissioning mothers. However, there is limited information on the experiences of surrogates (and partners), and the commissioning couple at the beginning stages of entering into a surrogacy program, and at key stages throughout the arrangement. In this prospective study we investigated the experiences of the commissioning couple and the surrogate and her partner, throughout the entire surrogacy process. Recruitment for this project has now completed and data analysis will commence in 2015.

Is Fresh Best?

Ilona Rose

Monash IVF, Clayton

Kelli Sorby

Monash IVF, Clayton

Prof Peter Lutjen

Monash IVF, Clayton

Dr Tiki Osianlis

Monash IVF, Clayton and Monash University, Clayton, Australia

Freezing all viable embryos during an IVF cycle, rather than transferring a fresh embryo, is being adopted in the clinic for multiple reasons, including to reduce the incidence of ovarian hyperstimulation syndrome (OHSS) and to improve birth outcomes for both mother and baby. However, there is concern pregnancy outcomes may be compromised utilizing this strategy. In this study we sought to determine whether a 'freeze only' strategy in IVF compromises cumulative pregnancy rates. This case controlled study of 181 patients undergoing freeze only cycles was conducted between January 2012 and August 2013 at Monash IVF. Controls were matched for age, number of egg collections, insemination type and usable embryos available for transfer and freezing on Day 5 and 6. There was no difference between case group and control for mean maternal age, number of egg collections and number of usable embryos. The pregnancy rates achieved in freeze only cycles were no different to those seen in fresh embryo transfer cycles whether considering pregnancy rate from first embryo transfer or cumulative pregnancy rates. The results of this study were presented at the 5th congress of the Asia Pacific Initiative on Reproduction (ASPIRE). It was awarded Best Clinical Paper.

Combined adjuvant therapy in IVF-ICSI

A/Prof Luk Rombauts

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Over the past 25 years, IVF has seen significant improvements, leading to much improved outcomes for many infertile couples. Nevertheless, a significant proportion of couples still experience the distress of repeated failure to conceive despite IVF. A history of repeated IVF failure presents a formidable challenge to the fertility specialist offering clinical guidance. By the time patients are convinced something must be wrong, they are often armed with online information from internet-based support forums and chat groups and insist on alternative approaches as they become increasingly desperate to try something new. Such alternative approaches are often based on a standard protocol with the addition of adjuvantia, such as aspirin, antibiotics, glucocorticoids or luteal phase estradiol supplementation, which have not been shown to provide clinical benefit in a significant number of studies. This project was a large case-controlled study investigating whether combined adjuvant treatment improves live birth rates in fresh and frozen IVF and intracytoplasmic sperm injection (ICSI) cycles. We found no benefit of this combined adjuvant strategy in fresh IVF cycles, and possible harm when used in frozen cycles. The results of this study were published in Reproductive BioMedicine Online.

Surgical sperm retrieval

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Surgical sperm recovery and ICSI often represent the optimal approach to conception in non-obstructive azoospermia (NOA) and many cases of obstructive azoospermia (OA). Micro-dissection testicular biopsy sperm extraction (micro-TESE) is widely held to be the 'gold standard' approach to testicular sperm retrieval, with reported higher sperm retrieval rates than traditional testicular biopsy sperm extraction (TESE). Micro-TESE requires significant specialisation, longer surgical time and more expense than TESE, making its access limited in some settings. We aimed to show that testicular sperm aspiration (TESA) and TESE in sequence can yield overall sperm retrieval rates comparable to those reported for micro-TESE. This retrospective multicentre, descriptive analysis of 155 men with NOA showed that in programs where micro TESE may not be available, acceptable sperm recovery rates can be achieved using this relatively low cost alternative that requires a widely available level of surgical skill.

Incidence and zygosity of twin births following transfers using a single fresh or frozen embryo

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Transferring a single blastocyst has been shown to significantly reduce multiple pregnancy rates and to increase the likelihood of delivering at term a single healthy baby. There is an acceptance that the incidence of monozygotic twin births is higher in the ART population compared with naturally conceived births. However, there are conflicting reports regarding treatment methods in ART and their involvement in increasing the twinning rate.

The aim of this study was to use gender discordance to estimate the monozygotic and dizygotic twinning rates following the transfer of single fresh or frozen embryo. Births from 4,701 fresh and frozen IVF/ICSI single embryo transfer (SET) cycles between 2007 and 2011 were retrospectively analysed. A total of 2.3% of the births were twins with 11.0% of these twins being of different gender. There was no difference in the twinning rate whether fresh or frozen embryos were used in either IVF or ICSI procedure. Furthermore, blastocyst transfer was not shown to increase the incidence of monochorionic - diamniotic twins. At least three quarters of twin births following a SET in a frozen cycle were discordant presumably due to a concurrent naturally conceived pregnancy. Patients should be advised to avoid intercourse prior to FET as twin pregnancy has a higher degree of risk and complication. These results were published in the journal Human Reproduction.

Decisions about confirmatory prenatal testing following preimplantation genetic diagnosis

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Preimplantation genetic diagnosis (PGD) is the process of genetically screening an embryo for either the correct chromosome complement or a specific inherited disorder to selectively transfer the genetically desired embryos to establish a healthy pregnancy. PGD allows the couple to be reassured from the beginning of the pregnancy that their child will be free of the genetic condition in the family or they will have a reduced risk of miscarriage due to aneuploidy and avoid the need for any prenatal testing. All couples who have PGD at Monash IVF are recommended to have prenatal diagnosis in a pregnancy following PGD. Testing of an established pregnancy, either by chorionic villus sampling (CVS) from 12 weeks gestation, or by amniocentesis (at 15-17 weeks gestation) are the diagnostic prenatal tests that offer a definitive genetic result for the fetus. Both of these procedures are invasive and have a very small risk of miscarriage associated with them (1% and 0.5% respectively). This retrospective study surveyed couples who had a baby born following PGD between January 2007 and December 2012 to determine if they proceeded with confirmatory prenatal testing as recommended and their reasons for doing so. This information will further enhance the service, advice and support given to couples undergoing PGD.

Utilisation of ART in Single Women and Lesbian couples since the 2010 change in Victorian legislation

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Enactment of the Assisted Reproductive Treatment Act (Vic) 2008 in January 2010 allowed single persons and same sex couples in Victoria to access reproductive treatments. The utilisation and acceptance of ART by single women and lesbian couples are both increasing. In this context it is important to identify the impact on ART resources.

The objective of this study was to observe trends in ART use amongst single women and lesbian couples prior to and following the change in legislation. Secondary objectives included identifying the type of treatment utilised (IVF or artificial insemination) and the type of sperm used (anonymous or known donor) A retrospective cohort analysis of Monash IVF patient's accessing ART after January 2010 was conducted, 1495 treatment cycles were included. A 103% increase in the utilisation of ART was observed amongst the single women group and a 245% increase in the lesbian couple population demonstrated a rapidly expanding patient base for ART exists amongst the single women and lesbian couple populations. Both groups were more likely to utilise anonymous donor sperm with 90.8% of treatment cycles using an anonymous donor sperm source. The results of this study were featured in the Australian and New Zealand Journal of Obstetrics and Gynaecology.

Effect of Corifollitropin-alpha on viable pregnancy rate in poor ovarian responders undergoing IVF treatment

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There is Level 1a evidence that corifollitropin-alpha (trade name, Elonva), a sustained-release gonadotropin, is a safe and equally effective alternative treatment to daily FSH injections in good prognosis patients. However, two pilot studies with Elonva in poor responders have shown no clinical benefit. In this observational study we investigated the efficacy and cost-effectiveness of corifollitropin-alpha in the largest cohort of poor responders to date. After adjusting for confounders, there were no differences in the embryo utilisation rate and viable pregnancy rate between the groups. However, the average cost per cycle for the corifollitropin-alpha cycles was markedly less than cycles with daily rFSH injections. This study demonstrated that antagonist cycles with corifollitropin-alpha achieve the same viable pregnancy rates in poor responders as daily FSH injections but at a 35% lower cost to the Australian Pharmaceutical Benefits Scheme.

Can you ever collect too many oocytes?

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The number of eggs retrieved following ovarian stimulation is often used as a surrogate outcome for clinical success. There have been several previous studies suggesting that beyond a certain number of oocytes collected the pregnancy rate in stimulated cycles with fresh embryo transfer starts to decline. This retrospective study investigated the association between the number of eggs retrieved during a stimulated cycle and clinical pregnancy and live birth outcome.

The data suggest that one cannot collect too many oocytes as both clinical pregnancy and live birth rates continue to increase as number of oocytes collected increases. Obtaining more embryos from one oocyte collection also increases the chance of cryopreservation and subsequent frozen embryo transfers and reduces the need for repeated ovarian stimulation and oocyte collections. The patient has a decreased risk of complications and a better chance of pregnancy. However, OHSS continues to be the commonest serious complication of COH and so this risk of must be considered when stimulation doses are decided. The results of this study were published in the journal of Human Reproduction.

Risk of placenta previa in ART births linked to endometrial thickness in Singleton births

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Placenta praevia is a term used to describe abnormally low placentation and is significant as it is associated with maternal and fetal complications. Known risk factors for placenta praevia include maternal age, multiple pregnancy, multiparity, smoking and drug use, and termination of pregnancy. A major reason for an increasing incidence of placenta praevia may be the rising number of Caesarean sections being performed. A less well-recognised risk factor is ART however, the underlying pathophysiology remains unclear. Varying theories have been developed ranging from hormonal effects on the endometrium, effects related to the embryo transfer and altered uterine contraction wave patterns.

This retrospective study investigated the association between endometrial combined thickness (measured prior to embryo transfer) and the relative risk of placenta praevia. We found that endometrial thickness in ART cycles is directly proportional to the risk of placenta praevia and that this risk is independent of significant risk factors, such as smoking and endometriosis, and is not due to increased serum oestradiol concentrations, parity or age. It is hypothesised that increased uterine peristalsis and placenta praevia may explain the observed increased risk of placenta praevia in ART and endometriosis. Further studies are planned to elucidate whether ECT is a surrogate marker of increased uterine contractility or altered endometrial receptivity.

Are Antagonist Protocols Less Optimal for use in Satellite IVF Clinics?

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Predictability of the egg pick up (EPU) date is of great importance for patients attending satellite clinics. Predictable EPU day allows patients and clinicians to coordinate IVF treatment cycles through the satellite clinics while minimising the time and financial burden of travelling into metropolitan cities for ongoing treatment. This study was conducted as a retrospective cohort analysis of agonist and antagonist treatment cycles conducted at two Monash IVF satellite clinics. Both clinics have an established EPU window of days 13 to 15 after commencement of stimulation. The number of treatment cycles was 1172, utilised by 959 patients. Data illustrated that antagonist treatment cycles have a high proportion of patient's requiring transfer to metropolitan clinics for EPU, with 3.6% of agonist cycle patients requiring transfer in comparison to 23.7% of antagonist cycle patients. Both groups showed a majority of EPU occurring within the day 13 to 15 window (72.8% agonist group, 62.2% antagonist group). However a higher proportion of antagonist cycles occurred outside the EPU window (27.2% agonist cycles, 37.8% antagonist cycles).

IVF success rate over the last decade

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Over the past decade, there has been a movement towards single embryo transfers (SET) to reduce the risk of multiple births and its associated complications. Some patients mistakenly believe that the chance of pregnancy is reduced with SETs, despite reports showing that replacing an elective single embryo increases the chance of a healthy term live birth compared to double embryo transfer. This study was carried out to demonstrate that success rates with IVF have been improving despite decreasing the number of embryos transferred.

This was a retrospective cohort study comparing live birth outcomes for women who started IVF between 2001 and 2005 with women who started between 2006 and 2010. The 2001-2005 cohort comprised 233 women and included a total of 1119 stimulated and frozen embryo transfer cycles. The 2006-2010 cohort consisted of 453 women and included a total of 1810 stimulated and frozen embryo transfer cycles. Life table analysis was used to evaluate cumulative live birth rates. Cumulative live birth rates demonstrated that the probability of a live birth by cycle six was 73.7% in the 2001-2005 cohort;

which significantly increased to 88.4% by cycle six in the 2006-2010 cohort ($p < 0.05$). There was an average of 1.8 embryos transferred per embryo transfer in the 2001-2005 cohort; which decreased to an average of 1.3 embryos transferred per embryo transfer in the 2006-2010 cohort.

The IVF success rate has significantly improved despite the number of embryos transferred being reduced, and in particular success rates among older women have increased. This study provides further support for elective SET.

ONGOING RESEARCH INTERESTS

Melatonin and infertility: Can we improve outcomes of assisted reproductive technology - a randomised placebo controlled trial

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During ART, eggs and embryos may interact negatively with oxygen molecules in a process called 'oxidative stress'. In recent years, interest has gathered regarding the role of oxidative stress on the quality of stored eggs and embryos, potentially reducing success rates and live birth rates following ART. It is proposed that melatonin, an endogenously produced antioxidant, may be able to help reduce the effect of oxidative stress on eggs and embryos.

The aim of this project is to determine whether oral melatonin supplementation can increase serum and follicular fluid levels of melatonin, reduce oxidative stress markers and improve ART outcomes. This is a double blinded randomised placebo controlled trial where women will receive varying doses of melatonin (in 3 subgroups) or a placebo (1 subgroup) during the first stimulated cycle from the time of stimulation injections up to egg collection. Data will be gathered looking at oocyte

number and quality, embryo number and quality, ultrasound Doppler flow to the ovaries and uterus, sleep patterns, pregnancy rates and live birth rates.

This is the first placebo-controlled RCT addressing these questions. If this study is successful, we would hope that melatonin would become a standard complementary therapy for all patients undergoing ART for infertility.

Proteomic analysis of receptive endometrium: identification of discriminative markers

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Although the success rates of IVF have risen considerably, problems with the implantation of the embryo into the lining of the womb (endometrium) limit the success in some women. During the normal menstrual cycle, implantation must occur across a ~4 day window because of hormonally-induced changes in the endometrium. These changes are not fully understood but we do know that they are altered in some infertile women. Furthermore, the drugs given to women during

IVF treatment also change the lining of the womb.

Defects in implantation are thought to be a major cause of poor ART outcomes and also to impact on placental function and the short and long-term health of offspring. Although success rates have risen over the years, typically 60-70% of embryos selected for transfer fail to implant. A common complaint from patients is that there are no reliable tests to reassure them that their endometrium is receptive.

We hypothesise that the profile of proteins secreted into the uterine cavity will indicate the uterine receptivity. These so called 'proteomic techniques' are being applied to endometrial tissue and uterine fluid in carefully selected groups of women and a number have already been identified. Long term we aim to develop a diagnostic test for use during infertility evaluation and to assist in modifying clinical protocols and in decision making for the clinicians.

Diagnostics for Endometrial Receptivity: harnessing a promising biomarker and exploiting a non-invasive method of sampling

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IVF has evolved into a suite of mainstream medical interventions to overcome infertility, yet implantation failure poses a critical limiting factor even when the embryos are carefully selected. This is of particular concern given that the use of IVF is increasing every year as women choose to have children at a later age. Implantation requires a synchronously developed healthy embryo and a receptive

endometrium. Endometrial receptivity is vital for implantation. Currently there is no test available to determine the status of endometrial receptivity at the time of embryo transfer. Development of diagnostics for endometrial receptivity is critical to improve IVF outcomes.

Our recent studies have identified a promising biomarker for receptivity. During the establishment of receptivity, a large part of a cell surface glycoprotein is released into the uterine cavity and its levels in the uterine fluid directly correlate with the status of receptivity, making this glycoprotein a promising biomarker for endometrial receptivity. Our next step is to establish a high throughput assay for this glycoprotein.

Our previous studies have relied on uterine lavage as the source of uterine fluid for receptivity tests. However, a number of intrinsic drawbacks are associated with uterine lavage collection and impose a critical gap in translating research discoveries into practice. Alternative methods of endometrial fluid sampling warrant investigation. Anatomically, the uterine cavity is directly connected to the cervical cavity; uterine secretions thus would be present in the endocervical fluids. Retrieving endocervical fluid is much easier and totally non-invasive. We are thus exploring the utility of endocervical fluids in the diagnosis of endometrial receptivity.

Endometrial receptivity: validating potential biomarkers in the uterine fluid and investigating fundamental biology on the uterine surface

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Embryo culture/selection/transfer techniques have advanced greatly, yet implantation failure still poses a crucial limiting factor. It is believed that the hurdle may lie in the “soil for the seeds”, the endometrium. Currently no biochemical tests are available for endometrial receptivity, and in ART practices embryos are transferred without knowing the status of the endometrium. Development of diagnostics for endometrial receptivity is critical to improve ART outcomes.

Our studies have identified a number of biomarkers for receptivity. In particular, 3 proteins warrant further investigation: PC6, a critical regulator for receptivity; α -DG-N, a protein released from the uterine surface into the cavity at receptivity; and PDGFAA, a growth factor newly identified as a potential receptivity biomarker in Dr Nie’s lab. We have established specific assays for PC6 and α -DG-N, whereas a PDGFAA ELISA is already commercially available. We aim to validate these 3 candidates in large cohorts of uterine fluids, comprising the first part of this proposal. In the second part of this proposal, we aim to uncover the fundamental aspects of endometrial epithelial receptivity.

Human trophectoderm-endometrial interactions: validating targets to facilitate implantation during IVF

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During embryo implantation blastocysts appose and firmly adhere to a receptive endometrium initiating implantation: adhesion leads to implantation failure/infertility. Whilst IVF is an important intervention for infertility, implantation failure is still a critical limiting factor for IVF success: alarmingly ~ 70% of IVF embryos fail to implant. There is very little known of human blastocyst-endometrial interactions largely due to ethical considerations in obtaining human material. Identifying the critical regulators at the time of implantation may identify targets to facilitate implantation during IVF.

To address this gap in knowledge we developed a unique model where we collected blastocyst conditioned media from clinical left overs from blastocysts that were transferred during IVF and either successfully implanted or did not implant. We used this media to treat primary human endometrial epithelial cells in vitro and demonstrated, for the first time, that IVF blastocysts release factors that alter endometrial adhesion and gene expression relative to implantation and pregnancy outcome during IVF (Cuman et al, 2013). Blastocysts that implanted after transfer in vivo facilitated adhesion while blastocysts that did not implant had no effect.

Our pilot studies have identified that small non-coding RNAs, microRNAs (miRs), were present in blastocyst conditioned media (BCM), and using miR array analysis we identified that the levels of certain miRs were differentially altered in blastocyst conditioned media from blastocysts that implanted compared to those that did not

implant. Extracellular miRs are known to be taken up by cells and alter cell function. We propose that blastocysts release miRs in vivo which regulate blastocyst-endometrial interactions during implantation. Blastocysts that are destined for implantation failure will release miR abnormally and will alter implantation and result in infertility. In the present proposal we aim to confirm our findings and determine the effect of the identified differentially altered miRs on trophectoderm-endometrial adhesion in vitro, the initiating event of implantation. This will provide functional in vitro evidence for the first time for whether targeting these interactions during embryo transfer may facilitate implantation.

MicroRNA in the embryo secretome as a non-invasive screening tool for aneuploidy

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Human oocytes display a high degree of aneuploidy and the rate of aneuploidy increases with age. Increasingly, women of advanced age are seeking ART and in this group of patients likelihood of success is low due to the low number of euploid oocytes available. Recently, there has been an increase in 24 chromosome screening for these patients to increase the likelihood of pregnancy by transferring known euploid embryos. The issue with any clinical chromosome screening is that it is a highly invasive and costly procedure requiring removal of cells from pre-implantation stage embryos. Rosenbluth et al (2012) recently showed that microRNA (miR) expression patterns differ in human blastocysts depending on their ploidy: aneuploid embryos appear to have a different expression patterns to euploid embryos.

This research examined miR expression in human blastocysts and blastocyst conditioned media (BCM) of patients scheduled for blastocyst biopsy aneuploid screening and determine whether miR expression profiles correlate with 24 chromosome aneuploid screening results. If there is a correlation, this may result in a non-invasive diagnostic test for aneuploidy that can be adopted by the wider IVF population. The principal aim of this study is to determine whether miRs in BCM from aneuploid and euploid blastocysts are differentially expressed. This will identify their utility as non-invasive markers of aneuploidy.

Do Endometrial Stem/Progenitor Cells Have a Role In Preparing a Receptive Endometrium?

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This observational study quantifies the concentration of adult stem cells in the endometrium of women undergoing IVF procedures. It correlates these with endometrial thickness (determined by ultrasound at the time of embryo transfer) and pregnancy outcome. Endometrial biopsies are collected in the cycle preceding the embryo transfer cycle and the epithelial progenitor cells (marker+) and mesenchymal stem cells (MSC, W5C5+) are quantified using specific markers we have identified. Our pilot data on 18 samples show 4 distinct sample groups; high concentrations of marker+ progenitors and W5C5+ MSC (n=5), low concentrations of both stem/progenitor cell types (n=4), high marker+ and low W5C5+ cells (n=1), and low marker+ and high W5C5+ cells (n=8). There were five subsequent pregnancies, all occurring in the latter group (P<0.01). Studies are ongoing to determine the robustness of this finding and to establish whether the women with high concentrations of W5C5+ and low marker+ cells have a thicker endometrium. Should this be demonstrated, a biopsy taken prior to embryo transfer may predict the likelihood of pregnancy on the basis of endometrial stem cell numbers.

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

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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 experienced, multidisciplinary team will use a mixed methods 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 of fetal abnormality, for a broad range of conditions, immediately following diagnosis.

The aims of this study are threefold: Aim 1 is to explore the psychosocial impact of a prenatal diagnosis of fetal abnormality on women. Aim 2 is to identify the social and professional supports utilised and needed by women at this time. Aim 3 is to 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. The project draws on a unique combination of

interdisciplinary investigators that has expertise in the provision of care e.g. obstetrics, genetic counselling, psychology, bioethics, law, and health professional education.

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

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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 prognostic significance of slow or fast EHR in naturally-conceived pregnancies has been well studied; however limited information is available for ART pregnancies.

The study aims to establish a normal range of embryonic heart rates at 7 weeks gestation in ART 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. This retrospective study is over a period of 2 years from 2007 to 2009, with all singleton pregnancies scanned between

6W1D and 7W6D will be included. The embryonic heart rates will be determined by M mode ultrasound. The range of embryonic heart rates will be evaluated to determine whether they form a normal distribution. The primary outcomes include successful first trimester pregnancy, confirmed by the standard 12 week ultrasound examination or miscarriage confirmed by ultrasound or medical documentation.

Studies on the genetic basis of male and idiopathic infertility, and the trans-generational health of children conceived through ART

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Male infertility is often due to the failure to produce adequate numbers of motile sperm capable of fertilisation. Infertility affects 1 in 20 Australian men and leads to approximately half of all ART treatments. 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. Based on our extensive mouse gene discovery

program, we have identified many genes with essential roles in male mouse fertility. As an extension of this work, and using a bioinformatics approach, we are systematically screening human male samples for mutations likely to cause infertility. Recent findings include an evolutionarily conserved association between Sertoli cell only syndrome in mice and humans, and mutations in the ETV5 gene.

During the current reporting period these studies have resulted in six publications in international peer reviewed journals, and several presentations at international and national meetings. Several other manuscripts are currently submitted for publication. In partnership this team and Monash IVF are internationally recognized for the contributions to andrology research and clinical practice.

Identification of novel marker proteins of spermatogenesis in human testicular interstitial fluid

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Infertility affects 1 in 20 men, and contributes to ~ half of ART therapy that overall now accounts for 3.6% of births in Australia. While genetic causes account for 25-35% of male infertility, the remaining 65-70% of cases is unexplained. In azoospermic men, surgery can recover testicular sperm for ICSI in 30-66% of patients, but there are no clinically relevant pre-operative parameters to identify which men might be spared a failed surgery and its related risks.

There is a clear need for new, less invasive methods to predict retrieval success from azoospermic men.

Using new proteomic strategies, we have discovered that testicular interstitial fluid (TIF) from a mouse model of non-obstructive azoospermia (NOA) contains numerous differentially-expressed proteins compared to controls. This finding opens the way to identify markers of spermatogenesis suitable for monitoring fertility status in NOA men. We hypothesise that one or more TIF proteins will act as candidate markers of sperm presence in infertile men. We aim to characterise differentially-expressed proteins in TIF collected from infertile men at the time of microsurgical -testicular sperm extraction (M-TESE). The ability to non-invasively monitor spermatogenesis using TIF marker protein(s) as a diagnostic has broad application in fertility regulation, including NOA.

Genetic causes of oligoasthenoteratospermia

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Male factor infertility is a sole or contributory factor to half of all ART cycles, yet many men are given a descriptive diagnosis based on semen quality rather than an actual cause. New strategies are needed to diagnose male infertility. This proposal seeks to expand our research program aimed at defining genotype-phenotype relationships in male infertility. We aim to identify genetic causes of oligoasthenoteratospermia (OAT), characterised by reduced sperm number, abnormal morphology and poor motility.

Our ongoing research has given us an excellent understanding of the biology of these processes and we are able to identify a large number of genes in which mutations are plausible causes of the OAT phenotype. We will perform Massively Parallel Sequencing of identified candidate genes involved in sperm head and/or tail development. These genes will be sequenced in a tightly defined cohort of OAT patients and fertile controls. This project will be the most comprehensive of its type to date, and may identify causal mutations in human OAT. This study will provide the basis for future research, in which the mechanisms by which particular mutations cause OAT will be defined using cell biological and genetic approaches and may lead to diagnostic protocols.

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

Dr Fabricio Costa

Monash Ultrasound for Women (MUFW), Clayton

Andrew McLennan

Sydney Ultrasound for Women (SUFW), Burwood

Dr Simon Meagher

Monash Ultrasound for Women, Richmond

Dr Melody Menezes

Monash Ultrasound for Women, Richmond

Prof Jon Hyett

Royal Prince Alfred Hospital (RPA), Sydney, Australia

ART pregnancies have reduced first trimester combined screening (FTCS) PAPP-A levels leading to an increased likelihood of receiving a false-positive result. On the other hand there is a significant difference in acceptance rate of prenatal diagnostic testing between women who conceive through ART and those who conceive spontaneously. Women who conceive through ART are less likely to opt for prenatal diagnosis even after controlling for confounding variables. In the last two years non-invasive prenatal testing (NIPT) with cfDNA appears to have some distinct advantages as a screening tool for trisomies 21, 18, and 13 in singleton pregnancies. The objective of this study is to assess the performance of screening by NIPT for trisomies 21 and 18 using a chromosome-selective sequencing method of cfDNA in maternal plasma obtained from an ART population undergoing routine screening at 11-13 weeks' gestation.

This prospective study includes data from ART patients attending routine FTCS at MUFW and SUFW between October 2013 and March 2014. A prospective chart review will be conducted to collect clinical data on these patients who will have undergone FTCS and NIPT. If they choose NIPT testing in addition to FTCS; testing will be performed at the same time as the gestational requirement of >10

weeks. A genetic counsellor from the clinics will report the test results to each patient. 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.

Long term health implications following IVF: a clinical and biological study of cardiovascular, metabolic and respiratory status in young adults

Prof Jane Halliday

The Murdoch Children's Research Institute, Parkville

A/Prof David Amor

The Murdoch Children's Research Institute, Parkville

Dr Sharon Lewis

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Prof Rob McLachlan

MIMR-PHI Institute of Medical Research and Monash IVF, Clayton

A/Prof John McBain

Melbourne IVF, Melbourne

cohort of 532 age- and sex-matched controls. We will undertake a pilot study involving the detailed clinical review of the cohorts to establish their cardio-metabolic and respiratory status in early adulthood using validated non-invasive assessment tools.

There is broad consensus that common adult-onset diseases have their origins in early life, possibly before birth, and that risk trajectories track through childhood until clinical disease manifests in adulthood. Children conceived through use of ART may be in a specific risk category. However, the long-term health implications of ART are largely unknown, as adequately powered and detailed studies are lacking. It is therefore of great importance to examine further the extent of specific longer-term risks of ART in relation to the development of common adult chronic diseases. We are uniquely placed to investigate the possible implications of ART on the risk of cardio- metabolic and respiratory diseases. We have already established a large, well-engaged and well-characterised cohort of 540 singletons (currently aged 19-29 years) born following ART, together with a

People's experiences of fertility preservation before cancer treatment

Prof Jane Fisher

Jean Hailes Clinical Research Unit, Monash University, Clayton

Dr Maggie Kirkman

Monash University, Melbourne

Dr Karin Hammarberg

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Prof Rob McLachlan

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A/Prof Kathryn Stern

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Dr Debra Gook

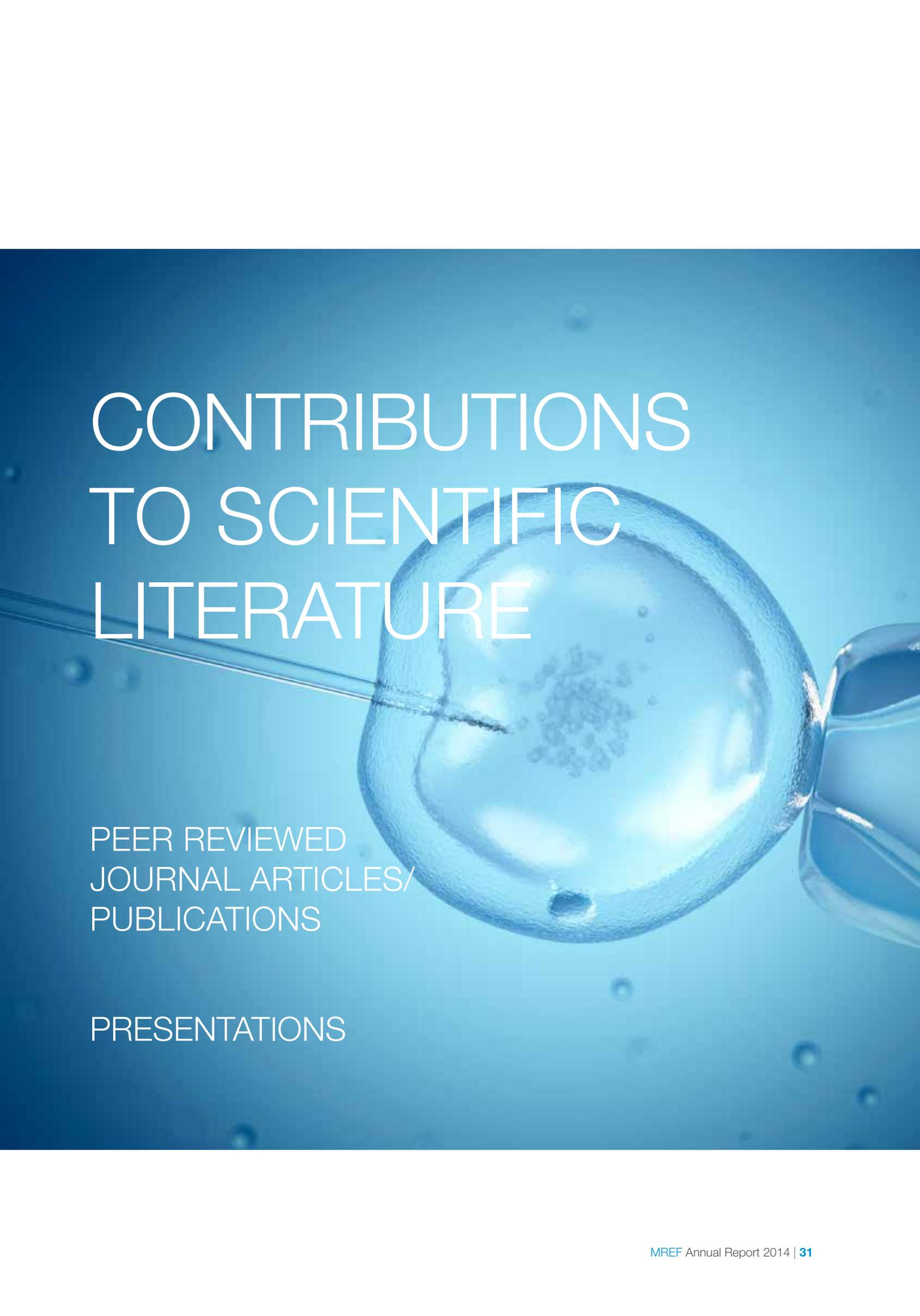
Dept Obstetrics and Gynaecology Royal Women's Hospital

Cancer treatment can have adverse effects on fertility. Fertility preservation before cancer treatment (through freezing of sperm, oocytes, ovarian tissue, testicular tissue, or embryos) is a service offered by some assisted reproductive technology (ART) clinics in Australia. Formal policies, protocols, clinical practices, and governance mechanisms develop in individual services as laboratory technologies advance. Australia does not yet have guidelines specific to fertility preservation for people with cancer, nor policies for organisations providing this service. The needs of patients who store reproductive material before treatment for cancer are poorly understood and there is scant evidence to inform best clinical practice for this emerging area of comprehensive care of patients with cancer and cancer survivors.

The significance for cancer survivors of reproductive material stored before treatment is inadequately understood, as are the reasons for continuing storage without using the material.

When survivors use their stored tissue and have a child, little is known about what it means to parent children born from reproductive material cryopreserved before cancer treatment.

This application is for the second component of the NHMRC-funded project 'Banking on the future: Establishing evidence for policy, protocols, and patient care relating to storage of reproductive material before treatment for cancer'. By surveying and interviewing adults who stored reproductive material before treatment for cancer, we aim to draw on their insights and experiences to inform the provision of fertility-related services and clinical care for people who are diagnosed with cancer during their reproductive years.

A microscopic image of a cell, possibly a zygote or embryo, with a pipette tip touching it. The background is a light blue gradient with some blurred cells.

CONTRIBUTIONS TO SCIENTIFIC LITERATURE

PEER REVIEWED
JOURNAL ARTICLES/
PUBLICATIONS

PRESENTATIONS

CONTRIBUTIONS TO SCIENTIFIC LITERATURE

The following compiles a portfolio of contributions to the scientific literature by Monash IVF staff and key collaborators for 2014. The list represents our commitment to a broad range of research interests spanning reproductive biology, genetic and molecular, andrology, clinical and psychological based research.

Peer Reviewed Journal Articles/Publications

1. **Becker CM, Laufer MR, Stratton P et al.** World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: I. Surgical phenotype data collection in endometriosis research. *Fertil Steril* 2014;102(5):1213-1222.
2. **Briggs R, Kovacs G, MacLachlan V, Motteram C, Baker HW.** Can you ever collect too many oocytes? *Hum Reprod*. 2014 Oct 31.
3. **Coughlan C, Ledger W, Wang Q, Liu F, Demirool A, Gurgan T, et al.** Recurrent implantation failure: definition and management. *Reprod Biomed Online*. 2014 Jan;28(1):14-38.
4. **Cuman C, Menkhorst E, Winship A, Van Sinderen M, Osianlis T, Rombauts LJ, et al.** Fetal-maternal communication: the role of Notch signalling in embryo implantation. *Reproduction*. 2014 Mar;147(3):R75-86.
5. **Eggers S, DeBoer KD, van den Bergen J, Gordon L, White SJ, Jamsai D, et al.** Copy number variation associated with meiotic arrest in idiopathic male infertility. *Fertil Steril*. 2015 Jan;103(1):214-9.
6. **Evans J, Hannan NJ, Edgell TA, Vollenhoven BJ, Lutjen PJ, Osianlis T, et al.** Fresh versus frozen embryo transfer: backing clinical decisions with scientific and clinical evidence. *Hum Reprod Update*. 2014 Jun 10.
7. **Fassbender A, Rahmioglu N, Vitonis AF et al.** World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project (EPHect): IV. Tissue collection, processing, and storage in endometriosis research. *Fertil Steril* 2014;102(5):1244-1253.
8. **Fernando S, Osianlis T, Vollenhoven B, Wallace E, Rombauts L.** A pilot double-blind randomised placebo-controlled dose-response trial assessing the effects of melatonin on infertility treatment (MIART): study protocol. *BMJ Open*. 2014;4(8):e005986.
9. **Fernando S, Rombauts L.** Melatonin: shedding light on infertility? - a review of the recent literature. *J Ovarian Res*. 2014 Oct 21;7(1):98.
10. **Fiske E, Weston G.** Utilisation of ART in single women and lesbian couples since the 2010 change in Victorian legislation. *Aust N Z J Obstet Gynaecol*. 2014 Oct;54(5):497-9.
11. **Halliday J, Wilson C, Hammarberg K, Doyle LW, Bruinsma F, McLachlan R, et al.** Comparing indicators of health and development of singleton young adults conceived with and without assisted reproductive technology. *Fertil Steril*. 2014 Apr;101(4):1055-63.
12. **Heng S, Dyonon K, Li Y, Edgell T, Rombauts LJ, Vollenhoven B, et al.** Development of a high throughput assay for human proprotein convertase 5/6 for detecting uterine receptivity. *Anal Biochem*. 2014 Dec 29.
13. **Holdsworth-Carson SJ, Zaitseva M, Girling JE, Vollenhoven BJ, Rogers PAW.** Common fibroid-associated genes are differentially expressed in phenotypically dissimilar cell populations isolated from within human fibroids and myometrium. *Reproduction*. 2014 Apr 8;147(5):683-92.
14. **Holdsworth-Carson SJ, Zaitseva M, Vollenhoven BJ, Rogers PAW.** Clonality of smooth muscle and fibroblast cell populations isolated from human fibroid and myometrial tissues. *Mol Hum Reprod*. 2014 Mar;20(3):250-9.
15. **Jamsai D, Lo JC, McLachlan RI, O'Bryan MK.** Genetic variants in the RABL2A gene in fertile and oligoasthenospermic infertile men. *Fertil Steril*. 2014 Jul;102(1):223-9.
16. **Kovacs GT.** What is new in IVF? *Med J Aust*. 2014 Sep 1;201(5):244-5.
17. **Lane M, Zander-Fox DL, Robker RL, McPherson NO.** Peri-conception parental obesity, reproductive health, and transgenerational impacts. *Trends Endocrinol Metab*. 2014 Dec 15.
18. **Osianlis T, Rombauts L, Gabbe M, Motteram C, Vollenhoven V.** Incidence and zygosity of twin births following transfers using a single fresh or frozen embryo. *Hum Reprod*. 2014 Jul;29(7):1438-43.
19. **Paule S, Nebel T, Webb AI, Vollenhoven B, Rombauts LJ, Nie G.** Proprotein convertase 5/6 cleaves platelet-derived growth factor A in the human endometrium in preparation for embryo implantation. *Mol Hum Reprod*. 2014 Nov 27.
20. **Piessens S, Healey M, Maher P, Tsaltas J, Rombauts L.** Can anyone screen for deep infiltrating endometriosis with transvaginal ultrasound? *Aust N Z J Obstet Gynaecol*. 2014 Oct;54(5):462-8.

21. **Rahmioglu N, Fassbender A, Vitonis AF et al.** WERF Endometriosis Phenome and Biobanking Harmonization Project (EPHect): III. Fluid biospecimen collection, processing, and storage in endometriosis research. *Fertil Steril* 2014;1233-1243.
22. **Rombauts L, Motteram C, Berkowitz E, Fernando S.** Risk of placenta praevia is linked to endometrial thickness in a retrospective cohort study of 4537 singleton assisted reproduction technology birthsdagger. *Hum Reprod.* 2014 Sep 19.
23. **Smith V, Osianlis T, Vollenhoven B.** A review of luteinizing hormone and its role in ovarian reserve testing. *Int J Reprod Contracept Obstet Gynecol.* 2014 3, 11-18.
24. **Swanson A, Griffin K, Brent R, Vollenhoven B.** Case-report: vaginal burn from alkaline battery in 8 year old. *J Pediatr Adolesc Gynecol* (in press).
25. **Van Sinderen M, Cuman C, Gamage T, Rainczuk K, Osianlis T, Rombauts L, et al.** Localisation of the Notch family in the human endometrium of fertile and infertile women. *J Mol Histol.* 2014 Dec;45(6):697-706.
26. **Vitonis AF, Vincent K, Rahmioglu N et al.** World Endometriosis Research Foundation (WERF) Endometriosis Phenome and biobanking harmonization project (EPHect): II. Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril* 2014;102(5):1223-1232

Presentations - International Conferences and Meetings

27. **Kaul V, Lolatgis N, Osianlis T, Sorby K, Vollenhoven B.** The use of intralipid in IVF cycles in poor responders with repeated implantation failure who were positive for NK cells. The European Society for Human Reproduction and Embryology; 2014, Jun 29 – Jul 2; Munich, Germany.
28. **Kaul V, Sorby K, Osianlis T, Jatkar S, Sultana F, Pritchard N, Sivapalan S, Vollenhoven B.** Improving endometrial receptivity: does hysteroscopy in the cycle prior help to improve implantation and clinical pregnancy. 70th Annual Scientific meeting of the American Society for Reproductive Medicine; 2014 Oct 18 – 22; Hawaii, USA.
29. **Heng S, Li Y, Paule S, Salamonsen L, Rombauts L, Vollenhoven B, Nie G.** The potential significance of post-translational regulation of glycoprotein dystroglycan in the human endometrium for embryo implantation. 61st Annual Scientific Meeting of Society for Gynecologic Investigation; 2014 Mar 26-29, Florence, Italy.
30. **Rombauts L.** Medical decision analysis as it could apply to endometriosis. World Endometriosis Society Consensus Meeting; 2014 April 30; Sao Paulo, Brazil. [Invited speaker]
31. **Smith V, Osianlis T, Vollenhoven B.** Luteinizing hormone and its role in ovarian reserve testing – a review. The Royal Australian and New Zealand College of Obstetricians & Gynaecologists New Zealand Committee Annual Scientific Meeting; 2014 Nov 13; Queenstown, New Zealand.

Presentations - National Conferences and Meetings

32. **Benz A, Osianlis T, Rombauts L.** Beyond the good prognosis patient: extended culture increases live birth rates for patients, regardless of quality and quantity of embryos on Day 3. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia. * ASPIRE award for Best Clinical Paper
33. **Beyer CE, Osborne E, Ryan J, Hamza K, Boyd S, Osianlis T.** Predicting segregation modes for Autosomal reciprocal translocations at Preimplantation genetic diagnosis. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
34. **Edgell T, Rombauts L, Vollenhoven B, Salamonsen L.** Endometrial Secretions; Predicting Receptivity Ahead of Embryo Transfer The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
35. **Heng S, Rombauts LJ, Vollenhoven B, Nie G.** Post-translational regulation of dystroglycan in the human endometrium for embryo implantation. Annual Scientific Meeting of the Endocrine Society of Australia and the Society for Reproductive Biology; 2014, Aug 24 - 27; Melbourne, Australia.
36. **Jamsai D, McLachlan R.** Genetic Variants in the ETV5 gene in fertile and infertile men with non-obstructive azoospermia associated with sertoli cell only syndrome. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.

37. **Pritchard N, Sorby K, Osianlis T, Kaul V, Vollenhoven BJ.** A case control study of melatonin in monotherapy and combination with co-enzyme Q10. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
38. **Talmor A, Nowak K, McLachlan V, Motteram C, McLachlan R.** Is micro-dissection testicular sperm extraction the minimum standard of care for non-obstructive azoospermic men? The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
39. **Rombauts L.** Endometriosis: New advances in clinical management. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 April 4-6; Brisbane, Australia. [Invited speaker]
40. **Rombauts L.** Cancer treatment and its effects on fertility. RANZCOG 2014 Victorian and Tasmanian Annual Scientific Meeting; 2014 Aug 16-17; Melbourne, Australia. [Invited speaker]
41. **Rombauts L, Larmour L, Aliabadi A, Motteram C, De Guingand D.** Health numeracy in fertile and infertile populations. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
42. **Rombauts L, Larmour L, Wallace E, Aliabadi A, Motteram C, De Guingand D.** Health numeracy and risk aversion in infertile patients. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
43. **Rombauts L, Motteram C.** Risk of placenta previa in ART births linked to endometrial thickness. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
44. **Rose I, Sorby K, Osianlis T.** Is Fresh Best? The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia. * Awarded Best Clinical Paper
45. **Sorby K, Osborne E, Osianlis T.** Aneuploidy Patterns in Blastocysts. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
46. **Costelloe K, Sorby K, Osianlis T.** Transportation of vitrified embryos using dry shippers – does it affect ART outcomes? The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
47. **Huston WM, Stansfield SH, Menon S, Allan JA, Weston G, Rombauts L.** Investigating of the potential use for the implementation of chlamydial serology during the initial infertility investigation. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
48. **Notini A, de Boer S, Cantsillieris S, Rossello F, Alers N, Kroushev A, Mockler J, Wallace E, Rombauts L, White S.** Defining the impact of assisted reproductive technologies on the placental Epigenome. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.
49. **Wade J, MacLachlan V, Kovacs G.** The success rate of IVF has significantly improved over the last decade. The 5th congress of the Asia Pacific Initiative on Reproduction; 2014 Sept 4-6; Brisbane, Australia.

Poster presentations - National Conferences and Meetings

MREF EXTERNAL RESEARCH GRANTS ATTRACTED IN 2014

Prof Robert McLachlan

NHMRC Research grants

2013 - 2015

NHMRC Project Grant #1042347 (2013-2015) Chief Investigator (CI).
“Establishing evidence for policy, protocols, and patient care relating to storage of reproductive material before treatment for cancer”

2013 - 2015

NHMRC Project Grant #1041949 Chief Investigator (CI).
“Leucine-rich guanylate kinase is a regulator of sperm tail development and motile cilia function”

A/Prof Luk Rombauts

NHMRC Research grants

2013 - 2015

NHMRC Project Grant #1044182, Chief Investigator (CI).
“Endometrial receptivity for embryo implantation: Proprotein convertase 6 and plasma membrane remodeling”

2013 - 2015

NHMRC Project Grant #1042347, Chief Investigator (CI).
“Establishing evidence for policy, protocols, and patient care relating to storage of reproductive material before treatment for cancer”

2013 - 2015

NHMRC Project Grant #1047056, Chief Investigator (CI).
“Changes in protein glycosylation promote endometrial receptivity leading to successful implantation”

A/Prof Beverley Vollenhoven

NHMRC Research grants

2014 - 2017

NHMRC Project Grant #1074342, Associate Investigator (AI).
“Melatonin and Infertility”

2013 - 2015

NHMRC Project Grant #1042347, Chief Investigator (CI). “Establishing evidence for policy, protocols, and patient care relating to storage of reproductive material before treatment for cancer”

2014 - 2017

ARC Linkage Grant.
“Elucidating the increasing demand for genital cosmetic surgery among girls and women in Australia”.

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- The MREF acknowledges with appreciation the support provided by MSD and Merck Serono Australia



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Clayton VIC 3168

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Monash IVF Richmond

Epworth Richmond
Level 7, 89 Bridge Road
Richmond 3121

T 03 9429 9188

Monash IVF Geelong

Geelong Private Medical Centre
Level 2, 73–79 Little Ryrie Street
Geelong VIC 3220

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- Bendigo Day Surgery
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