Melbourne ART abd Health meeting 14/02/2023

The aim of the meeting was to bring together collaborators with the Eueopean Research Council funded A.R.T-HEALTH programme from Australia, New Zeland, Singapore, China and Japan to meet in person and share previous and on-going research projects and plans.

Brief notes for each session:

Speaker	Title	Summary Notes
Jane Halliday Sharon Lewis Sarah Biggs	Welcome A history of research at the MCRI on ART outcomes	To gain knowledge of general and reproductive health outcomes for adults conceived by ART, we surveyed a cohort of males and females, aged 27-38 years, conceived using IVF or GIFT, and compared them with spontaneously conceived (SC) age-matched controls. The survey was completed by 234 IVF-conceived, 76 GIFT-conceived and 153 SC adults. Our findings suggest that ART conception does not appear to adversely affect general health in adult males or females. Although there was no increase in reproductive health conditions in ART-conceived males, we did observe an overall increase in self-reported female reproductive health conditions, driven by a nominal increase in endometriosis. The prevalence of endometriosis, however, was still within the population norm for this condition. We will further explore a possible increase in clinically diagnosed endometriosis in future studies of ART-conceived adult females.
Boris Novakovic	Epigenetic data in the CHART cohort, titled: 'The epigenetic legacy of Assisted Reproductive Technology'.	The presentation summarised genome-wide DNA methylation analysis of adults conceived through ART, published in Nature Communications in 2019, and subsequent replication of findings in multiple studies. Overall, we have clear evidence that DNA methylation is altered at specific regions of the genome in individuals conceived by ART, but it is still unclear if a particular ART procedure or the underlying fertility and/or genetics, are the main drivers of the epigenetic change. In current work, the team at MCRI are exploring the role of DNA methylation in adverse pregnancy outcomes, and are continuing with adult analysis, with the HIM cohort, a DNA methylation dataset of men conceived by ICSI.
Deborah Lawlor	The ART-HEALTH project overview & future plans	A.R.T Health is a programme of research funded by the European Research Council. It aims to determine the effects of conception by assisted reproductive technology (ART) on offspring perinatal and subsequent health. This is being done by triangulating evidence from different

		study types (including (i) a collaboration of birth cohorts from across the world, including from Australasia, in which people conceived by ART and those from natural conception are recruited and followed-up in identical ways, with no selection on conception method and similar information on confounders, but may lack detailed information on specific ART treatments (ii) health care record linkage studies from different countries that have large numbers and and littile missing data but might have limited information on confounders and ART tretments and (iii) clinical (ART) studies that may have no or highly select (friends and family) compariton groups) and analytical methods. The aim that where results are similar across different study types and different analysis methods with different key sources of bias that increases confidence in that being the the correct causal effect. As well as exploring potential effects on offspring health outcomes the aim is also to explore mechanisms (e.g. metabolomic and epigenomic). A key aims is to support a global partnership who can work together in this area. The meeting enabled key input from colleagues in Australia, China, Japan and New Zealand (see above and below), highlighting several years of translational research and the importance of working together to understand effects of ART, different types of ART on offspring future health. In this way the meeting was complementing the earlier kick off meeting in the UK which because of time differences was difficult to get input from these groups.
Jonathan Huang	GUSTO	The Growing Up in Singapore Towards healthy Outcomes (GUSTO) longitudinal family cohort (N = 1450) is now in its 14th year of follow-up with relatively high retention (N ~900). Singapore is a dense, wealthy, island nation-state located in Southeast Asia with a diverse population drawing from Chinese, Malay, and Indian ancestries, and our cohort reflects this. Detailed information on our design and variable-level data including repeated clinical and research measures on physical and mental health and development in mothers, children, and fathers along with biobank-derived measures that are analysis-ready or planned can be found at https://gustodatavault.sg/ . Highlights include multi-tissue, multi-omics and infant and child brain and body MRI. ART and IVF- related work include target trial investigations of epigenetic mediation and on-going work on placental transcriptomics. We are also eager to

		partner on other areas of research including environmental exposures, paternal effects, causal inference methods, and beyond.
Kenji Tsuchiya	HBC study	Birth cohort studies in Japan 1. Hamamatsu University School of Medicine, Research Center for Child Mental Development 2. Osaka University United Graduate School of Child Development tsuchiya@hama-med.ac.jp; Handaya 1 Higashiku, Hamamatsu 4313192, Japan In 2019, six birth cohort studies in Japan formed a consortium and started a collaborative research project: The Japan Birth Cohort Consortium (JBiCC). In the Autumn of 2022, a new member joined JBiCC bringing the total to seven, with a total of 50,000 children being followed for development. One member of JBiCC, the Hamamatsu Birth Cohort for Mothers and Children (HBC Study), has a sample of 1,138 mothers and 1,258 children followed up from birth to 13 years and onward. The HBC Study is characterized by frequent face-to-face assessments, neurodevelopment in particular (Takagai et al., Int J Epidemiol 2016). The cohort involves 87 (7%) and 20 (2%) children born from IVF and ICSI, respectively. All the biological fathers of these children are the partners of the mothers of the children. All the members of JBiCC are keen to collaborate with the members of the A.R.T-HEALTH project.
Susan Morton	GUiNZ	Growing up in New Zealand https://www.growingup.co.nz/ is a large prodpective birth cohort that has followed ~6,000 children and their families since 2009-2010 when their parents were recruited during the mothers pregnancy. The study has secure funding to follow the offspring into adulthood (at least 21 years of age). The study has maintained a close relation to the government so that findings can influence policy. They are very keen to remain involved with the A.R.T. Health programme and contribute to understanding the potential effects of ART on future health.

		Prof Susan Morton has moved to Australia to become the Director of the Institute for Innovative solutions for well being and health (INSIGHT) at the University of Technology Sydney. Professor Sarah-Jane Paine will be the key contact person for GUNZ involvement in the programme going forward
Wan Teh	Natural or hormonal stim cycles for frozen -thawed embryo transfer?	'IVF is a medical treatment for infertility. As a fertility specialist who deals with infertile patients on a daily basis, I feel reassured to see the recent data on health outcomes of IVF-conceived individuals (compared to naturally conceived controls). To further minimize any potential risks of this medical treatment, I feel that we need to investigate whether different treatment protocols/medications/lab interventions have any impact on offering outcomes. There are a lot of data on pregnancy rates, but very little on offspring health outcomes between different interventions in IVF. Currently, we have some data on fresh versus frozen embryo transfers. Very limited data on different frozen embryo transfer protocols. No information on different stimulation protocols/drugs/lab techniques. The IVF world has moved on from just pregnancy outcomes. Further evidence is required to help guide clinical practice to make IVF a safer medical treatment. '
Sarah Catford	ICSI-conceived male offspring: reproductive and metabolic health	**Reproductive and metabolic health of ICSI-conceived young men** **Key points** • Almost 65% of all IVF cycles worldwide use ICSI. • Concerns include transgenerational inheritance of male infertility, effects of poor-quality sperm on non-gonadal aspects of offspring health and potential for technique to induce epigenetic changes with long-term health consequences. • Metabolic study ○ ICSI-conceived men had higher resting diastolic blood pressure and HOMA-IR scores compared to naturally conceived (NC) men.

		○ Mixed results in literature regarding cardiovascular risk from IVF and ICSI conception. ○ Findings require further validation. ○ The metabolic profiles of singleton ICSI- and IVF- conceived men were similar. ○ Subgroup analysis suggests that paternal infertility does not influence metabolic risk in sons. • Reproductive study ○ Largest study so far of semen parameters and reproductive hormones in ICSI-conceived men. ○ Minor differences of uncertain significance in sperm progressive motility and morphology. ○ Sperm output and concentration, total motility, and total motile count similar between ICSI-conceived men and NC controls. ○ Overall, these results are reassuring and suggest that ICSI-conceived men are likely to have comparable reproductive health to their peers conceived naturally. • Future research will need to consider potential sources of bias, parental characteristics, and technological variations in ART procedures over time.
Kiri Beilby	Animal studies on ART offspring outcomes	Animal studies allow us to study the use of ARTs in healthy animal populations and remove the chicken vs egg issue of parent health and subsequent offspring health after the use of assisted reproduction. As such, we conducted a systematic review and meta-analysis that included studies conducted in any mammalian species where at least one postnatal outcome was measured, and an in vitro intervention (IVM, IVF, ICSI) was used alongside an in vivo conception arm (natural conception or artificial insemination). Studies that matched our criteria were found in 61 studies across 5 different animal species (sheep, cow, mouse, non-human primate, horse). Birth weight and gestational age were significantly different between in vivo vs in vitro offspring, demonstrated predominantly through bovine studies. While data was too heterogeneous or few for all other postnatal physiological measurements reported, there were also indications that ART impacts metabolic, cardiovascular and behavioural aspects of offspring born in healthy animal populations. These data provide evidence for us

		to proceed with care regarding the use of ARTs in human populations and call for more data to be collected, but also for more heterogeneity in how we collect data on various physiological outcomes.
Rui Wang	IPD meta-analysis INFORM: Freeze-all embryo transfer – what is new?	Freeze-all embryo transfer – what is new? Dr Rui Wang, Department of Obstetrics and Gynaecology, Monash University Individual participant data meta-analysis has been considered the gold standard for evidence synthesis and it provides an opportunity to provide evidence to support personalised care. However, this type of projects is time consuming and resource intensive. The INFORM project is an individual participant data meta-analysis comparing frozen and fresh embryo transfer. It involves a collaboration consisting of investigators across eight countries to share de-identified trial data. Rui provided a progress overview of the INFORM project over the past 18 months and presented an analysis of two cases during the data sharing to demonstrate the challenges for data sharing due to the lack of governance and over governance.
Anthea Lindquist	Safety and long-term implications of adjunct (unregulated) medications used in IVF - state and national linkage	Building on previous research in the field, our population-wide linkage study aimed to investigate the school-age developmental and educational outcomes for children conceived via IVF, compared with their spontaneously conceived peers. Our findings were reassuring, finding no significant difference between the groups in the outcomes measured (Australian Early Development Census at age 4-6 years and NAPLAN at age 7-9). The main question that remains is whether different IVF techniques, specifically ICSI vs standard IVF and fresh vs frozen embryo transfer, confer different developmental and educational outcomes for the children conceived. Our new program of work will use the same population-wide data, linked further with PBS prescribing data to investigate the maternal and childhood outcomes following the use of adjunct medications in IVF treatment
Amber Kennedy	School age outcomes after IVF	A population wide health record linkage study led by Amber, suggests that school-age developmental and educational outcomes for children conceived by IVF are equivalent to

		those of spontaneously conceived children. The findings provide important reassurance for current and prospective parents and for clinicians.The paper can be found at https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1004148