Reproductive Medicine

ue to the ongoing COVID-19 pandemic, 2021 continued to present a number of challenges, particularly during lockdown in the first quarter. Nevertheless, reproductive medicine services, including assisted reproduction services, were facilitated and provided by specialists at the National Maternity Hospital (NMH), Merrion Fertility Clinic (MFC), St. Michael's Hospital (SMH) and our satellite clinic in Galway.

A. ESHRE Accreditation

In 2021, MFC/NMH received accreditation by the European Society for Human Reproduction and Embryology (ESHRE) as an ESHRE/EBCOG (European Board and College of Obstetrics and Gynaecology) affiliated subspecialist training centre in Reproductive Medicine and Surgery. This important recognition of our subspecialty training program will formalise training at a senior level in Reproductive Medicine and will make trainees eligible to become European Fellows of Reproductive Medicine (EFRM). The inspection team were extremely impressed with our facilities and training program and awarded us accreditation for 5 years, rather than the standard 2 years they generally award for first inspections. This accreditation is a testament to the dedicated and experienced staff at MFC and the NMH.

B. Increased activity Merrion Fertility Clinic

Referrals and treatments at Merrion Fertility Clinic increased significantly in 2021 compared to the previous 2 years. This is likely related to the clinic's increasing public profile and reputation and a planned expansion of services. However, it is also likely to be related to the covid pandemic which may have led to an increased focus generally on fertility and the importance of family. Difficulty travelling abroad for treatment may also have contributed. Activity in 2020 was curtailed by the clinic's closure for over 2 months in 2020 due to the Covid pandemic.

Compared to 2020, referrals in 2021 increased by 42%, total oocyte retrievals increased by 57%, oocyte vitrification cycles increased by 143%, IVF/ICSI cycles increased by 47.5%, Frozen embryo transfer cycles increased by 59% and IUI cycles increased by 300%.

C. COVID-19, Telehealth and patient e-learning digital platform

As a result of the continuing global COVID-19 pandemic, mitigation strategies including video patient consultations, telemedicine, restricted access for partners and enhanced infection control measures remained in place. This enabled a full continuation of services. Telehealth was expanded to include a secure online e-consent platform for ART related procedures.

D. The Childhood Cancer Fertility Project (MFC and Irish Cancer Society)

The Childhood Cancer Fertility Project was launched jointly with the Irish Cancer Society in August 2020, MFC having been successful in securing grant funding from the Irish Cancer Society for a three-year project (2020-2023) to develop and provide fertility preservation for children, adolescents and young adults. A sperm and egg freezing service for post-pubertal adolescents about to undergo gonadotoxic treatment is now well established and a post-treatment assessment and treatment clinic has been established for survivors aged up to 24. In September 2021, a team from MFC visited the John Radcliffe Hospital in Oxford, which has a world renowned ovarian and testicular tissue cryopreservation service for pre-pubertal children. Collaboration and expert advice from our colleagues in Oxford will help MFC to establish a similar service in Ireland.

E. Merrion Fertility Foundation (MFF)

A very generous donation was received to our sister charity, the Merrion Fertility Foundation. This will enable us to provide assistance to many more patients in the coming years.

Clinical Activity Clinic appointments

Dedicated hospital clinics for reproductive medicine, encompassing infertility, endometriosis, PCOS etc continued throughout 2021 with 304 first visits, 131 return appointments, 183 telephone/telemed consultations. Our recurrent and multiple miscarriage clinics saw 40 women/couples and did 44 new telephone/telemed consultations.

The mean age of women undergoing fresh IVF/ICSI cycles was 37.4 years. In 2021, 30.1% of all cycles started were in women aged 40 or more, an increase of 9% over 2019 and 2020. See Chart 1.

Elective single embryo transfer eSET: 65,7% of MFC patients had a single embryo transfer in 2021, reflecting the clinic's strong single embryo transfer policy. Of this group, a subset of good prognosis patients had an elective single embryo transfer (eSET), meaning they had a top or good quality embryo to transfer and at least one other to freeze. This group comprised 36.7%

of all embryo transfers and, across all age groups, had a clinical pregnancy rate per embryo transfer of 46.2% on the fresh cycle. Of those eSET patients who did not conceive on their fresh cycle, 52.5% conceived on their first frozen embryo transfer (FET), bringing the cumulative pregnancy rate in this group to 84.6% (following one fresh transfer and a FET if the fresh was unsuccessful). Many of these patients have additional embryos still in storage.

Multiple pregnancy: The multiple pregnancy rate following a fresh embryo transfer was 2.6%, a rate which is very low by international standards. All of these multiple pregnancies were twins and the majority (92.3%) occurred following double embryo transfer (6.25% multiples vs 0.3% in SET group).

Livebirth rates are the best marker of ART success and are reported for 2020 as, at the time of writing, not all 2021 pregnancies are complete. The livebirth rates per embryo transfer for fresh IVF and ICSI cycles performed in 2020 (delivering in 2020/2021) are excellent by international norms (Table 4, Chart 2). Approximately one third of all couples completing IVF/ICSI cycles had a livebirth.

Frozen embryo transfer (FET) cycles: In 2021, the clinical pregnancy rate per embryo transfer for frozen embryo transfer cycles increased significantly. This may be due to changes in luteal phase support with greater use of subcutaneous progesterone, particularly in those with a history of prior biochemical pregnancy. See Chart 3, Table 5.

Intrauterine Insemination (IUI): In 2021, the overall clinical pregnancy rate per intrauterine insemination was 13%. This figure includes IUI using donor-derived sperm (see below). The clinical pregnancy rate for IUI where a partner's sperm was used was 7.6%, with 92 inseminations completed and 7 clinical pregnancies recorded in 2021.

Donor Sperm treatments: Merrion Fertility Clinic commenced a donor sperm service in 2018. Sperm is sourced from two approved donor banks in Denmark. This is an essential treatment for single women, same sex couples and heterosexual couples with severe male factor infertility, not suitable for ICSI ± Surgical Sperm Retrieval. This is a growing and successful service. See Tables 6 and 7.

Child, Adolescent and Young Adult (CAYA) Fertility Preservation Services

AYA Males: Twelve adolescent males between the ages of 12 and 17 years were referred to MFC in 2021 for sperm cryopreservation services before undergoing gonadotoxic treatment or surgery for cancer (11 patients) or autoimmune disease (1 patient). Diagnoses included: melanoma, testicular tumour, T-cell acute lymphoblastic leukaemia (ALL), Hodgkin's lymphoma, Burkitt's lymphoma, osteosarcoma, acute myeloid leukaemia (AML) and rhabdomyosarcoma. Of these 12 boys, 11 produced a semen sample and all 11 had sperm of suitable quality for freezing.

AYA Females: Three adolescent females (aged 15 to 17 years) were referred to MFC in 2021 for oocyte vitrification before undergoing gonadotoxic cancer therapy. Oncology diagnoses were oligodendroglioma and Hodgkin's Lymphoma. All of these young women had a successful cycle, with a mean of 7 oocytes cryopreserved for future use.

Six female survivors of CAYA cancer, who had previously received gonadotoxic treatment as part of their cancer therapy, attended MFC in 2021 for an initial fertility consultation. Thirteen female survivors attended for a follow-up fertility consultation and ovarian reserve testing.

Research

The Reproductive Medicine department maintains an active and productive research portfolio, collaborating with scientists in Irish academic institutions such as UCD and TCD. MFC employs a full-time Research Officer and two Clinical Research Fellow posts exist for higher training in Reproductive Medicine & Surgery, with both fellows undertaking higher degrees. An additional Aspire Fellowship post was filled in 2021. MFC also hosts PhD and MSc students.

Research at MFC is aimed at improving knowledge, expertise and care pathways in the field of reproductive medicine. Our studies span a range of topics, from basic mechanistic biology to clinical translational research. In 2021, researchers at MFC also worked closely with collaborators at several of Ireland's leading academic research institutions, including University College Dublin and Trinity College Dublin, on the following research projects:

- Innate immune factors, endometrial receptivity and
 infertility (Funding: Grant for Fertility Innovation, Merck)
- Endometrial microbiome and infertility (Funding: Grant for Fertility Innovation, Merck)

- Glycome analysis in endometriosis (NIBRT collaboration. Funding: Horizon 2020, Marie Curie International Fellowship)
- Development of improved laboratory tests for sperm quality and function in male infertility (Funding: Irish Research Council)
- Knowledge and attitudes towards fertility preservation

among patients and healthcare providers

- Ovarian reserve in childhood cancer survivors
- Impact of the COVID-19 pandemic, fertility service postponement and clinic risk mitigation strategies on fertility patients
- Attitudes of male fertility patients towards the novel COVID-19 vaccine

Publications are in the Published Research section.

Table 1: Reproductive surgery under General Anaesthetic

Reproductive surgery at NMH	2021
Hysteroscopy - operative and diagnostic	86
Operative laparoscopy	29
Diagnostic laparoscopy	39
Myomectomy	3
Total laparoscopic hysterectomy	4

Table 2: Assisted Reproduction, Merrion Fertility Clinic

Year	Semen analyses	Surgical Sperm Retrievals	Ovulation induction and IUI (completed)	IVF/ICSI (Completed to oocyte retrieval)	Frozen embryo transfer cycles (Completed to embryo transfer)	Oocyte vitrification Completed to oocyte retrieval)
2017	1398	8	157	454	263	3
2018	1459	2	151	407	301	40
2019	1412	6	161	399	334	49
2020	1172	9	152	413	236	46
2021	1426	10	226	609	376	112

Conscious sedation was provided by Consultant Anaesthetists for all oocyte retrievals and surgical sperm retrievals.

Table 3: Activity and Clinical pregnancy rates (%) for IVF and ICSI cycles

2021	All Ages	Under 35	35-37	38-39	40-41	42-44
Cycles Started (n)	687	141	166	173	135	72
Oocyte Collections	609	126	151	153	120	59
Embryo Transfer	498	96	126	127	101	48
Average Eggs Collected	7.89	9.83	7.92	7.59	6.55	7.22
Clinical Pregnancies	179	36	51	47	30	15
CPR per Cycle Started	26.1	25.5	30.7	27.2	22.2	20.8
CPR per Oocyte Collection	29.4	28.6	33.8	30.7	25	25.4
CPR per ET	35.9	37.5	40.5	37	29.7	31.3

Clinical pregnancy rates as per ESHRE (European Society for Human Reproduction and Embryology) i.e. fetal heart, fetal pole or a clear pregnancy sac are seen on ultrasound at 6 to 8 weeks gestation. Biochemical pregnancies (positive pregnancy test only) are not included but ectopic pregnancies and miscarriages are.

Table 4: Live Birth Rate fresh IVF/ICSI 2020

	All Ages	Under 35	35-37	38-39	40-41	42-44
LBs	100	37	22	25	13	3
LBR per OCR	24.75%	32.46%	21.57%	27.78%	19.70%	9.38%
LBR per ET	31.55%	44.05%	26.51%	35.21%	23.64%	12.50%

Chart 1: 2020 Clinical Pregnancy Rates by Maternal Age

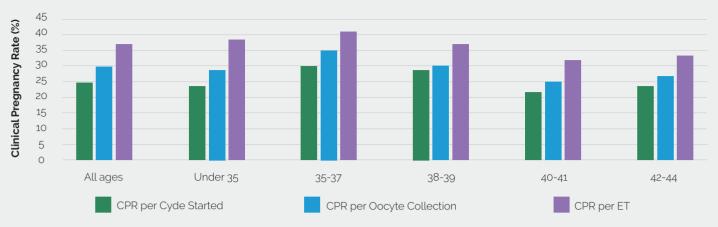


Chart 2: Live Birth Rate (2020) per Fresh Embryo Transfer by Maternal Age

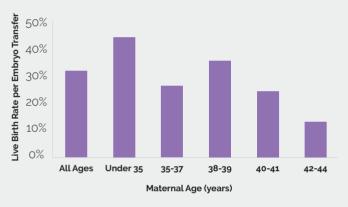
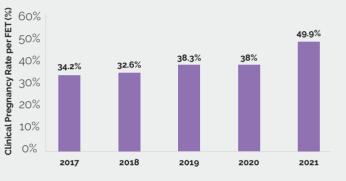


Chart 3: Five-year Clinical Pregnancy Rate (%) per Frozen Embryo Transfer (FET)



Frozen embryo transfer (FET) cycles: In 2021, the clinical pregnancy rate per embryo transfer for frozen embryo transfer cycles increased significantly. This may be due to changes in luteal phase support with greater use of subcutaneous progesterone, particularly in those with a history of prior biochemical pregnancy. See Chart 3, Table 5.

Table 5: Live Birth Rates Frozen Embryo Transfer 2020

Table 5: Live Birth Rates Frozen Embryo Transfer 2020		Table 6: Clinical Pregnancy Rates	Table 6: Clinical Pregnancy Rates (%) for IUI cycles using Donor Sperm			
2020	All Ages	2021	All Ages			
Thaws	315	Cycles started	48			
Embryo Transfer	313	Inseminations	36			
Live Births	76	Clinical Pregnancy	7			
LBR per Thaw	24.10%	CPR per cycle started	14.6			
LBR per Embryo Transfer	24.28%	CPR per insemination	19.4			
		Multiple rate	0			

Table 7: Clinical pregnancy rates (%) for IVF and ICSI cycles using Donor Sperm

2021	All Ages	Under 35	35-37	38-39	40-41	42-44
Cycles Started	25	2	6	8	8	1
Oocyte Collections	21	2	5	6	7	1
Embryo Transfer	17	1	5	3	7	1
Clinical Pregnancies	6	0	2	0	4	0
Multiple Pregnancies	1	0	0	0	1	0
Average Eggs Collected	8.8	16	8.4	8.83	6.1	15
CPR per Cycle Started	24.0	0.0	33.3	0.0	50.0	0.0
CPR per Oocyte Collection	28.6		40.0	0.0	57.1	0.0
CPR per ET	35.3	0.0	40.0	0.0	57.1	0.0
Multiple Rate	6				14.3	

PUBLISHED RESEARCH Articles, Editorials, Letters

ANAESTHETICS

Glennon K, Donnelly J, Knowles S, McAuliffe FM, O'Reilly A, Corcoran S, Walsh J, McMorrow R, Higgins T, Bolger L, Clinton S, O'Riordan S, Start A, Roche D, Bartels H, Malone C, McAuley K, McDermott A, Inzitari R, O'Donnell CPF, Malone F, Higgins S, De Gascun C, Doran P, Brennan DJ. Immunological assessment of SARS-CoV-2 infection in pregnancy from diagnosis to delivery: A multicentre prospective study. PLoS One. 2021 Sep 20;16(9):e0253090. doi: 10.1371/journal. pone.0253090. eCollection 2021. PMID: 34543278

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Invited Lectures

L Hartigan

Future Fertility for Young People with Cancer ICLO-NLS (Irish Circle of Lacanian Orientation) Congress 'Wanting a Child? Desire for Family and Clinic of Filiations', April 2021

L Hartigan

Fertility preservation and contraception (before/during/ after treatment) RCPI Acute Medicine Series: Hot Topics in AYA Haemato-Oncology Webinar, August 2021

229

L Hartigan

Fertility: what are my options? CAYA Survivor Conference, September 2021

M Wingfield

Ovarian Tissue Cryopreservation and the Childhood Cancer Fertility Project

ESHRE Campus Workshop on Reproductive Tissue Engineering and Fertility Preservation, September 2021

A Giblin

Attitudes of Healthcare Professionals to Draft National Legislation on Assisted Human Reproduction (AHR) Student Summer Research Awards (SSRA), UCD School of Medicine, October 2021

S O'Brien and L Glover Science of Fertility Cavan-Monaghan Science Festival, November 2021

L Glover Reproductive Immunology TU MSc Clinical Immunology, November 2021

L Schaler

ERA (endometrial receptivity array) Testing Sharing Best Practice (SBP) Conference, November 2021

L Hartigan, L Glover, H Groarke, M Wingfield, L O'Shea Follicular fluid levels of IL-10 influence fertilisation and early embryo development Fertility 2021, Virtual Conference 6-10 January 2021

F Giangrazia, D Crosby, F Reidy, M Wingfield, L Glover, C O'Farrelly

Dysregulation of IL-17A and calprotectin in the female reproductive tract affects pregnancy outcome following assisted reproductive therapy Fertility 2021, Virtual Conference 6-10 January 2021

M Horan, L Glover, M Wingfield Managing fertility in young patients with endometriosis -- how are we doing? Fertility 2021, Virtual Conference 6-10 January 2021

L Schaler, M Horan, M Wingfield A review of spontaneous pregnancies and patient behaviour during the first wave of SARS-CoV-2 Fertility 2021, Virtual Conference 6-10 January 2021 F Reidy, L Glover, J Leyden, J Cullinane, M Wingfield Embryo development in endometriosis: A study of timelapse imaging Fertility 2021, Virtual Conference 6-10 January 2021

Z Kovács, Y Xie, B Adamczyk, F Reidy, F Mcauliffe, P Rudd, M Butler, M Wingfield, L Glover, R Saldova Procainamide fluorescent labeling for identification of low abundant non-invasive glycan biomarkers Society for Reproductive Investigation (SRI) 68th Annual Meeting, 6-9 July, 2021

D Roche, F Martyn, M Wingfield Fertility treatment and live birth are still possible following the unexpected diagnosis of endometrial carcinoma/complex hyperplasia provided that there is careful multidisciplinary team involvement ESHRE virtual 37th Annual Meeting, 26 June - 1 July, 2021

Z Kovács, B Adamczyk, F Reidy, F McAuliffe, PM Rudd, M Wingfield, L Glover, R Saldova Novel non-invasive diagnostic options for endometriosis - based on glycome analysis ESHRE virtual 37th Annual Meeting, 26 June - 1 July, 2021

F Reidy, F Giangrazi, C O'Farrelly, M Wingfield, L Glover The expression of innate immune factors in the eutopic endometrium of women with Endometriosis ESHRE virtual 37th Annual Meeting, 26 June - 1 July, 2021

L Schaler, L Glover, M Wingfield COVID-19: Fertility patients' attitudes to pregnancy and implemented changes within fertility services during a pandemic

ESHRE virtual 37th Annual Meeting, 26 June - 1 July, 2021

M Horan, L Glover, P Downey, M Wingfield Knowledge of women undergoing surgery for endometrioma regarding the impact of the disease and its treatment on ovarian reserve and fertility. ESHRE virtual 37th Annual Meeting, 26 June - 1 July, 2021

Procainamide fluorescent labeling for identification of low abundant non-invasive glycan biomarkers Z Kovács, Y Xie, B Adamczyk, F Reidy, F Mcauliffe, P Rudd, M Butler, M Wingfield, L Glover, R Saldova 21st European Carbohydrate Symposium (Eurocarcb21), 18-22 July, 2021 L Schaler, L Glover, M Wingfield Covid-19 And Fertility: The Toll on Mental Health IOG and JOGS Annual Meeting 2021, 26 November 2021

A Giblin, L Schaler, L Glover, M Wingfield Attitudes of Healthcare Professionals to Draft National Legislation on Assisted Human Reproduction (AHR) In Ireland ()

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L Schaler, L Glover, M Wingfield Male Fertility Patients attitudes to the COVID-19 Vaccine IOG and JOGS Annual Meeting 2021, 26 November 2021

S O'Brien, L Schaler, L Glover, M Wingfield Assisted Reproduction: a Luxury for the "Rich" and a Debt Weight for the Poor

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